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ORIGINAL ARTICLES.

FOCAL INFECTIONS IMPLICATING THE NERVOUS SYSTEM.

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The work of Orr, Rows and others during the past 25 years has revealed to us some of the avenues by which the central nervous system is reached by infections which usually are contiguous in origin to the point of the nervous system attacked, but may often be remote. The general idea that pneumonia may be complicated by a myelitis, that periapical abscess may cause inflammation of distant nerves or roots, such causes and effects are sufficiently familiar to us all. I shall then hardly be able to tell you any new thing, but can point out how the disease picture is determined inevitably by the anatomical pattern so that almost distinct syndromes are evolved. Toxic products or bacterial content pass along set channels: their ultimate destinations are fixed only by tissue barriers and humoral resistance, as the protective dikes of the organism.

One or two characteristic cases will illustrate my meaning:

Case Reports. Case 1.—A woman in her middle thirties reported monthly attacks of herpes in the skin area supplied by the second and third lumbar roots on the left side. The condition was accompanied by severe pain and appeared on the second or third day before each menstrual period. This phenomenon had been recurring for 2 years. My associate, S. B. Wortis, not content with a dermatologic explanation, discovered a fairly large and infected Bartholin's cyst on the same side as her herpes. We advised surgical excision of this focus. However, she suffered 6 attacks of premenstrual herpes before taking action. Nine months ago she had an attack of herpes and radicular pain before the period following the operation, since when she has been entirely free of symptoms.

TABLE 1.—PATHWAYS OF INFECTION. TONSILLITIS WITH REFERRED PAIN.
Of 182 cases of tonsillitis, 18 (9.9 per cent) had referred pain.

Case.	Sex.	Age.	General symptoms.	Physical exam.	Neurological.	Referred pain.	Organism.	Complication.	Outcome.
1661 .	M	25	Cough	T (espe. L); P.; CN + (L)	Neg.	Chest; L. ear	Pneumoc. (tonsillar smear)	None	Imp.
1675 .	M	21	None	T; CN + (bilat.); R. ear drum red	Neg.	R. neck; R. ear	Omitted	?Early mitral disease	Imp.
1690 .	M	35	Cough	T; P; CN + (bilat.); chest râles	Neg.	Under L. ear	Omitted	None	Imp.
1697 .	F	19	Malaise	T; P	Neg.	Neck; R. ear	Omitted	None	Imp.
1700 .	M	30	Rigor	T; P; CN + (esp. L)	Neg.	Neck; both ears; both sides of face	Omitted	None	Imp.
1616 .	M	20	Rigor; cough; herpes, lips; bl. sputum	T; P; CN +	Neg.	Front of head; R. ear	Smear neg.	None	Imp.
1584 .	F	39	Cough	T; CN + (bilat.)	Aj's: O	L. chest; under R. ear; along R. sternomastoid	Omitted	Varicose veins; pregnancy?	Imp.
1590 .	M	24	None	T	Omitted	R. jaw and down R. neck	Many cocci and bacilli (smear)	None	Imp.
1592 .	F	53	None	T; P; CN +; perf. both ear drums	Neg.	Front of head; pain L. eye	Omitted	Acute glossitis	Imp.
1611 .	M	30	Rigor	T; P; CN + (bilat.); L. frontal sinus tender (X-ray neg.)	Neg.	Severe frontal; shooting pains, both ears	Omitted	None	Imp.
815 . .	M	46	Rigor; malaise; gen. pains	T; CN +	Neg.	L. chest	Omitted	Conjunctivitis, acute	Imp.
830 . .	M	23	Rigor; gen. pains	T; P; CN +	Neg.	L. chest	Omitted	None	Imp.
835 . .	M	24	Rigor; malaise; sweating; gen. pns.; bl. sput.	T, esp. R; P; CN + (R)	Deep refl. incr.	Chest; R. ear and R. neck	Omitted	None	Imp.
836 . .	M	29	Rigor; cough; vomiting	T; P	Neg.	L. chest	Omitted	None	Imp.
837 . .	M	20	Rigor; malaise; cough	T	Neg.	Chest	Omitted	None	Imp.
839 . .	M	25	Cough; herpes, lip	T; P; L	Neg.	R. chest	Omitted	None	Imp.
840 . .	M	64	Rigor; cough	T; P	Pupils sluggish; deep refl. incr.	Chest	Omitted	None	Imp.
844 . .	M	30	Malaise; cough; gen. pns.	T (esp. L); P	Neg.	Chest	Omitted	None	Imp.

T = tonsillitis; P = pharyngitis; L = laryngitis; CN + = cervical nodes enlarged.

TABLE 2.—PATHWAYS OF INFECTION. TRANSVERSE MYELITIS.

Of 137 cases of transverse myelitis, 7 (5.1 per cent) were secondary to infection. (Trauma, lues and alcohol, etc.; in most cases the cause was undetermined.) No organisms isolated, except S. aureus in Case 19.

Case.	Sex.	Age.	Type of infection.	Pathway.	Spinal cord level.	Duration: 1. From onset. 2. Duration of T. M.	Blood.		Urine.	Spinal fluid.	Outcome.
							W. B. C. (in thousands per c.mm.) and Differential (per cent).	R. B. C. (in millions per c.mm.), Hb. (per cent) and Blood chem.			
50	F	33	Pyelonephritis	Lymph or blood	D5	1. ? 2. 370 days	W.B.C. 12.0 P. 85	R.B.C. 0 Hb. 80	1015 Pus +++	Alb. +; glob. +; tp 35–59.6; cg and Wassermann neg.	Died
51	F	28	Pneumonia (broncho)	Blood	T2–6 Ascending cord softening	1. 76 days 2. ?Imp. after 95 days	W.B.C. 7.7 P. 65 L. 26 Tr. 6 Pme 3	R.B.C. 3.4 Hb. 60 N.P.N. 35 Sug. 80	1038 Negative	cg 221100; sug., glob., Wassermann neg.	Imp.
43	M	55	Pneumonia (uveitis)	Blood	D5–L1 Ascending cord softening	1. 35 days 2. 58 days	W.B.C. 21.0 P. 87	R.B.C. 2.5 Hb. 55 Bl. chem. ng.	1016 Alb. vft.	Bloody (prob. traumatic); decr. pr.	Died
16	M	41	Embolism (thrombosed internal hemorrhoids)	Blood	D6	1. ? 2. 48 days	W.B.C. 7.2 P. 70 L. 20 Tr. 8 Eos. 2	Bl. chem. ng.	1010 Alb. +	Glob., sug. and Wassermann neg.	Died
28	F	22	Abortion (septic)	Blood	Mid-dorsal	1. 5–6 mos. 2. Present on discharge; never out of bed after abortion	W.B.C. 13.0 P. 63 L. 27	R.B.C. 4.3 Hb. 85	Neg.	0	Unimp.
19	F	20	Septicemia (infected finger)	Blood	D6	1. 8 days 2. 18 days	W.B.C. 30.4 P. 87	R.B.C. 0	1009 1017 Alb. tr.	Evid. of block; Froin syndrome; cells 100 p. cc.; glob. ++++ Staph. aureus	Died
7*	M	33	Septicemia (infected finger)	Blood (cult. sterile 8 wks. later)	D2	1. ? (chill 8 wks. ago)	W.B.C. 16.0 P. 82	R.B.C. 4.78 Hb. 75	1020 Neg.	Pr. incr.; cells 27; glob. and sug.	Died

* Roentgen ray finger: osteoperiostitis.

TABLE 3.—PATHWAYS OF INFECTION. DIPHTHERIA.

No skin diphtheria found. Of 294 cases of diphtheria, 13 (4.4 per cent) showed involvement of the nervous system.

Case.	Sex.	Age.	Focus of infection.	Culture.	Paralysis; with days after onset in parens.	Antitoxin given; days after onset in parens.	Outcome; days after onset that paralysis cleared up in parens.
5728 . .	M	4½	T	Pos.	P (33); MC	20,000 U. (1) 10,000 U. (3)	47 (death)
3438 . .	M	27	T	Pos.	P (21); E (?); PN (?); MC	20,000 U. (21) 10,000 U. (42)	P and E? (148); ?PN
1286 . .	M	5	T; N	Pos.	P (8)	20,000 U. (4)	P? (24)
341 . .	M	2½	T; N	Pos.	P (11); MC	15,000 U. (2)	P? (31)
5668 . .	M	8	T	Pos.	P (20)	25,000 U. (5)	P (62)
3518 . .	M	1½	T; N; L	Pos.	P (42); E (?); PN (?); neck weak	30,000 U. (3)	P (74; E? (74); PN? (74)
4934 . .	M	2½	T	Pos.	P (38); PN (38)	20,000 U. (3)	41 (death)
1378 . .	M	5	T; N	Pos.	P (11); E (50); MC	5,000 U. (2) 10,000 U. (3) 5,000 U. (4)	P and E until death (56)
3192 . .	F	3	T; N	Pos.	P (18); PN and incontinence (?)	25,000 U. (8)	P (52); PN and still incont. on discharge
861 . .	M	19	T; N	Pos.	P (40); E (40); PN (59)	30,000 U. (3)	P and E (54); PN present on discharge (79)
899 . .	F	5	T; N	Pos.	P (12); peripheral facial (12); E (9); MC	15,000 U. (4)	14 (death)
2255 . .	F	2	T; N	Pos.	P? (27); PN? (27); MC; neck weak	20,000 U. (4)	46 (death)
? . . .	M	3	T	Pos.	P? (21); PN (42); back weak	10,000 U. (1)	While in hospital

T = throat; N = nose; L = larynx; P = palate; E = Eye; PN = peripheral neuritis; MC = myocarditis.

CASE 2.—A man seen in the middle West some years ago was presented as a case of amyotrophic lateral sclerosis. For 2 months he had had progressive ascending weakness of the legs with so-called rheumatic pains and disturbance of sphincter control. Wasting and fibrillary twitching of the thigh muscles were dominating features of his condition. Nothing abnormal was found in the arms, a peculiarity which, added to bladder involvement and shooting pain in the legs, cast doubt on the original diagnosis. A rectal examination gave evidence of a firm but fluctuating mass in the prostate which was correctly diagnosed as abscess and evacuated. Complete sphincter control was reëstablished within a month and progressive recovery in motor function followed.

CASE 3.—A middle-aged officer had 8 teeth removed, following local novocain infiltration of the gums. Three days later he began to suffer from severe pain in the back of the neck and violent headache. Progressive signs of meningitis developed, which were confirmed by finding streptococci in the spinal fluid. Death occurred within 3 weeks despite the giving of antimeningococcus serum and frequently repeated blood transfusions.

It may be said here that the morbid process in these cases could scarcely have been recognized had not the general plan of drainage

TABLE 4.—PATHWAYS OF INFECTION. CAUDA EQUINA NEURITIS.

The following cases are selected from 765 cases of "neuritis," *i. e.*, all forms of neuritis except polyneuritis.

Case.	Sex.	Age.	Focus of infection.	Organism.	Probable pathway.	Sp. cord segments or peripheral nerves involved.	Onset after focal infection: Time interval.	Laboratory.	Roentgen ray.	Operative findings.	Outcome.
315*	F	16	Probably perineal infec.	? Gc (pos. vag. smear infec. 2 mos. prev.)	Lymph	S1–4	5 mos.	Temp. 103.6°; alb., pus; R. B. C. 3.6 million; hb. 70%; W.B.C. neg.; bl. chem. neg.	.....	Swollen, glossy, red roots with adhesions	Slight imp. after oper.
296	M	45	Influenza	?	? Blood	Approx. L1	Immed. after influenza 8 yrs. prev.	Temp. 100.2°; bl. not done	Sl. hypertr. arthr.; L5 vert.	No oper.; lum. punc. neg.	Unimp.
370†	F	43	?	?	Prox. inflam. reaction	Lower lumbosacral	Immed. after hysterectomy 4 yrs. prev.	Temp. 101°; alb. ++; few W.B.C.; bl. count not done; bl. Wass. neg.	Suggestive lesion, L5 vert.	No oper.	Unimp.
169‡	M	55	?	?	?	L5–S1	(?) Symps. 7 mos. before adm.	Temp. 104°; Alb. ++; W.B.C. and R. B. C.; W. B. C. 14,200; P85, T5, L10	.....	Agglut. C.-E. route; pseudo tumor	Imp. after oper.
215	M	70	Influenza	?	? Blood	Lumbosacral roots	(?) Immed. after exposure to bad weather	Temp. 98.8°; bl. Wass. neg.; bl. chem. neg.	Not done	No oper.	Unimp. after 3 days in hosp.
221	F	40	Influenza	?	Blood	Lumbosacral roots	(?) Immed. following influenza 3 mos. prev.	Temp. 97–99°; pus; R.B.C. 3.23 millions; hb. 80%; bl. chem. neg.	Disuse atrophy of long bones	No oper.	Imp. after 84 days
230	M	28	Influenza	?	Blood	Lumbosacral radiculitis	(?) Following influenza 1 yr. prev.	Temp. 99°; R.B.C. 5.32 million; hb. 86%; bl. Wass. neg.	Pelvis and spine neg.	No oper.	Imp. after 11 days

* Surgically proven case. † Bony disease. ‡ Surgically proven case. Lumbar puncture negative. Lipiodol showed obstruction level L4.

TABLE 5.—PATHWAYS OF INFECTION. MENINGITIS SECONDARY TO INFECTIONS ABOUT THE HEAD.
Of 422 cases of meningitis, 24 (5.7 per cent), were secondary to infection about the head.

Case.	Sex.	Age.	Site of infection.	Organism: 1 = Primary infection. 2 = Spinal fluid. 3 = Blood.	Involvement of nervous system.	No. of days after infection meningitis appeared.	Pathway.	Treatment.	Outcome.
67 . .	F	8	Abscess, L. eyelid; panophthalmitis	1. Staph. 2. Neg. 3. Gram-pos. dip.	Cav. sinus thrombosis; meningitis	5th day	Lymph or blood (venous)	Antimening. serum 6th day; incis. abscess	Died 9th day
84 . .	M	15	Abscess of upper lip	1. Staph.? 2. Gram-pos. cocci 3. Staph.	Cellulitis of face; meningitis	Approx. 7th day	Lymph or blood	No serum	Died 9th day
50 . .	M	29	Furuncle of L. nose	1. Staph.? 2. Neg. culture 3. Staph.	Cav. sinus thrombosis; meningitis	3d day	Lymph or blood	No serum	Died 5th day
73 . .	F	12	L. ear	1. Omitted 2. Strep. and staph. (smear) 3. Omitted	Epidural abscess (oper.); meningitis	O. M. P. C., sev. mos.; convulsions night before	Direct or lymph or blood (venous)	No serum; mastoidectomy	Died 21 days after adm.
88 . .	F	37	Abscess of L. ear	1. Omitted 2. Omitted 3. Omitted	Meningitis	O. M. P. C., 27 days	Direct or lymph or blood (venous)	No serum	Died about 33d day
8 . .	F	10	Cellulitis of R. orbit	No tap or culture (prob. strep.)	Meningitis	2d day	Lymph or blood	No serum	Died 5th day
59 . .	F	34	O. M. P. A., bilat.	1. Hemol. strep. and staph. 2. Non-hemol. strep. 3. Omitted	Meningitis	Approx. 14th day	Direct or lymph or blood	No serum; bilat. myringotomy	Died 28th day
65 . .	M	15	O. M. P. C., R.; abscess in front of R. ear	1. Strep. (swab from oper.) 2. Gram-pos. pneum. (confirmed by mouse injection) 3. Neg.	Softening of brain tissue (?abscess)	? 7th day	Lymph or blood	No serum; abscess drained	Died 46th day

69 . .	M	6½	O. M. P. A., R.	1. Staph. aureus 2. Nonhemol. strep. 3. Omitted	Meningitis	Approx. 14th day	Direct or lymph or blood	No serum; mastoidectomy	Died 25th day
53 . .	M	57	Carbuncle, R. neck (angle of mandible)	1. Staph. aureus? 2. Neg. 3. Staph. aureus	Meningitis	295th day	Lymph or blood	No serum	Died 301st day
7 . .	M	49	Carbuncle back of neck	1. Neg. 2. Neg. 3. Not done	Osteomyel., epimening., mening., myelomal. (P.M., R. cerebell. and spinal cord C4–5)	12th day	Lymph	No serum; decompr. laminec.	Died 61st day
10 . .	M	14	O. M. P. A., L.	1. Pneumo. (smear) 2. Gram-pos. diplo., mostly extracell. 3. Omitted	Meningitis (P.M., green fluid at base)	5th day	Direct or lymph or blood	No serum	Died 5th day, 3½ hrs. after adm.
18 . .	M	59	O. M. P. A., L., foll. extract. of carious teeth	1. Pneumo. (P.M., ear) 2. Pneumo. (smear) 3. Omitted	Meningitis (P.M., pneumo. mening. fluid over brain)	3d day	Direct or lymph or blood	No serum	Died 7th day
19 . .	M	24	Abscess of L. cheek foll. extract. of tooth	1. Omitted 2. Omitted 3. Omitted	Septicemia; spin. fluid clear; ?abscess of brain	12th day	Blood	No serum	Died 22d day
20 . .	F	62	P. M. P. C., R., with acute exacerb.	1. Pneumo. (P.M.) 2. Pneumo. 3. Omitted	Meningitis (P.M., leptomening. of base)	2d day	Direct or lymph or blood	No serum	Died 6th day
21 . .	M	31	Furuncle in L. ear	1. Neg. 2. Neg. 3. Omitted	Serous meningitis (sterile)	Approx. 31st day	Lymph or blood	No serum	Neur. neg. 79th day; otitic hydrocephalus

TABLE 5.—PATHWAYS OF INFECTION. MENINGITIS SECONDARY TO INFECTIONS ABOUT THE HEAD.—(*Continued.*)

Case.	Sex.	Age.	Site of infection.	Organism: 1 = Primary infection. 2 = Spinal fluid. 3 = Blood.	Involvement of nervous system.	No. of days after infection meningitis appeared.	Pathway.	Treatment.	Outcome.
13 . .	F	28	O. M. P. A., L.	1. Omitted 2. Pneumo. 3. Neg.	Meningitis	Ca. 7th day	Lymph	No serum	Died 8th day
17 . .	M	26	L. cheek, acute purulent maxillary sinusitis	1. Omitted 2. Omitted 3. Neg.	Upper cord? toxic from myelitis; sp. fluid 15 cells; anesth. L. face; neck stiff	Ca. 9th day	Lymph or blood	No serum	Died 56th day
20 . .	F	35	Ulcer R. cheek; max. sinu. foll. extraction of teeth; cellulitis R. orbit	1. Pneumo. (P.M.) culture 2. Pneumo (P.M.) 3. Neg.	Meningitis (P.M.)	Ca. 20th day	Direct or lymph or blood	No serum	Died 22d day
43 . . (D1)	F	28	O. M. P. A., bilateral	1. Omitted 2. Staph. and strep. (smear) 3. Omitted	Extradural absc.	Ca. 60th day	Direct or lymph	No serum; mastoidectomy, bilateral	Died 63d day
43 . . (D3)	M	42	O. M. P. A., R.	1. Strep. 2. Strep. 3. Omitted	Meningitis	No history, patient in coma	Direct or lymph or blood	No serum; myringotomy, R.	Died within 24 hrs. after adm.
5 . .	M	50	O. M. P. A., L.	1. Pneumo. (P.M.) 2. Pneumo. (P.M.) 3. Omitted	Meningitis	No history, patient in coma	Direct or lymph or blood	No serum	Died within 24 hrs. after adm.
10 . .	F	38	O. M. P. A., R.	1. Omitted 2. Strep. hemolyticus (smear and cult.)	Meningitis(P.M.), ac. pur. mening.	18th day	Lymph or blood	No serum	Died 21st day

pathways to the nervous system from infected areas been previously hypothecated and later proven. Indeed, one feels that the comparative paucity of infecting foci found in our Bellevue groups of nervous system infections may be due to the absence of the correlation of cause and effect in the minds of the examiners.

In a careful reading of the records of 182 cases of acute follicular tonsillitis, there were found 18 (9.9 per cent) in which severe referred pain was a prominent symptom. All such cases were adults, probably because children localize pain poorly. The distribution of pain was in order of frequency: the ears (local disease was absent), the chest wall, the face and neck. In short, these severe referred pains occurred in the area of distribution of the fifth nerves and the upper cervical roots. An appreciation of the significance of these pains would make needless many puncturings of normal eardrums and sinuses.

A review of 294 cases of nasopharyngeal-laryngeal diphtheria admitted to Willard Parker Hospital and treated with antitoxin at varying intervals from the beginning of the disease showed that 4.4 per cent had involvement of the nervous system. The symptoms in the order of frequency were palatal palsy, palsy of accommodation, polyneuritis. Death in most cases was attributed to myocarditis.

Nearly all these neural cases were heavily treated—20,000 and 30,000 units—but too late. Apparently, absorbed diphtheria toxin combines readily with nervous tissue and forms a stable product, in that subsequent enormous doses of antidiphtheritic toxin avails little to reduce neural symptoms. Some of the polyneuritic cases complicating diphtheria were difficult to differentiate from poliomyelitis, in that thoracic and cervical radiculitis produced weakness of related muscle groups and sacral root involvement occasionally resulted in sphincter paralysis.

No cases of skin diphtheria could be found as such in the Bellevue or Willard Parker records. However this aspect has been well studied by Walsh in troops on active service in Egypt. Here so-called "desert-sores" occurred commonly from which Klebs-Loeffler bacilli were recovered in almost pure culture. A vast number of cases of polyneuritis ensued.

The most important observation made by Walsh was that invariably there was an initial local paresis related anatomically to the site of the infected focus, a fact which forbids the notion that in such conditions the toxin is carried entirely by the blood to the nervous tissue. No case of extrafaucial diphtheria had paralysis of the palate.

Two of his cases may be mentioned here:

Case 4.—An artillery driver suffered from multiple septic sores on the thighs and buttocks and a large ulcer of the perineum. After 7 weeks he began to have numbness on the buttocks and around the anus. This numbness spread to the penis, scrotum, and the backs of the thighs; a few days

later there was loss of control of the bladder and rectum. Not until weeks afterward was there general polyneuritis, by which time there was also deterioration of visual convergence. On examination, he was found to have complete loss of all forms of sensation over the 4th and 5th sacral root areas and partial loss over the 2d and 3d sacral root areas.

CASE 5.—A medical officer infected his right thumb while performing a tracheotomy on a fatal case of laryngeal diphtheria. The finger wound healed in 7 weeks, but he began to notice numbness and loss of feeling in the affected thumb; this numbness spread to the radial part of the hand. Also ataxia and weakness developed in the right arm. After these disabilities he sustained a generalized multiple neuritis, but had no accommodation paralysis.

An examination of the Bellevue records of 765 cases diagnosed as neuritis (but not including polyneuritis) revealed a group of 7 cases of severe cauda equina neuritis 5 of which immediately followed influenza; 1 case was secondary to gonococcal infection of the perineum, and another followed hysterectomy. I feel sure that ascending neuritis of the cauda equina occurs more frequently than hospital records would seem to show; suspicious cases in the gynecologic and urologic fields should be rigorously examined.

Of 137 cases of transverse myelitis studied, 5.1 per cent were secondary to a known infection; in most cases the cause was undetermined. Pneumonia was responsible for 2 gradually ascending softenings on the dorsal cord. Two upper dorsal transverse lesions were secondary to infected fingers. A thrombosed internal hemorrhoid furnished the focus in the fifth case and a septic abortion in yet another. It would appear that in this group the blood stream is the path of access to the spinal cord; the dorsal cord would seem especially susceptible to attack and one remembers that this also holds good for Pott's disease of the spine.

Infections about the head accounted for 5.7 per cent of 422 cases of meningitis studied from the Bellevue records. Fifteen were secondary to infections of the middle ear; 1 of these was a case of serous meningitis with hydrocephalus; 2 followed orbital infections; 2 followed carbuncle of the neck and 2 sinusitis; 1 came from a cheek abscess and 1 from a furuncle of the nasal mucous membrane. The last proceeded from a cellulitis of the upper lip.

With the exception of the case of otitic hydrocephalus, all were fatal: a mortality which emphasizes the necessity of treating infections about the upper face by wet dressings and drainage rather than by incision.

The details of these cases are presented in chart form. These neural complications of focal infection are nothing more than the commonplaces of hospital experience; to know that they occur in bulk will impose on us the need of search for prime causes in conditions apparently more obscure.

NOTE.—My sincere thanks are due Miss Sarah Shiras for her great help in the statistical investigation of several thousand case records.

TUMORS OF THE GASSERIAN GANGLION.*†

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(From the D. J. McCarthy Foundation of the University of Pennsylvania.)

The severe symptoms accompanying tumors of the Gasserian ganglion have resulted in recognition of the condition for many years. Among the earliest case reports, Sachs[1] has mentioned 1 by Dixon in 1846 and 1 by Günsburg in 1848. Peet[2] refers to a primary tumor studied as early as 1836, by R. W. Smith, and reported in 1849. Peet found a total of 63 cases in the literature in 1927. Additional cases are 1 of Parker,[3] 2 reported by Russell,[4] a case of Rand,[5] 2 of Altmann,[6] 1 of Gaines,[7] 1 of Learmonth and Kernohan,[8] Bradley and Smith[9] and 1 which was studied in the respective services of Dr. Spiller and Dr. Frazier and reported by the author.[10] Cadwalader[11] has reported a tumor which arose in the immediate neighborhood of the Gasserian ganglion and completely embraced the sensory root, causing symptoms characteristic of a tumor arising in the ganglion itself. This gives a total of 76 reported tumors, including Peet's 2 cases and the 1 of Cadwalader.

Tumors of the Gasserian ganglion are relatively rare. Frazier[12] had performed major operations on more than 300 patients suffering from tic douloureux up to 1918 and at that time had encountered only 3 instances of tumor involving the Gasserian ganglion. Cushing,[13] in 1920, had found 4 primary and 4 secondary tumors causing symptoms referable to the ganglion in his series of 550 verified intracranial tumors. In the files in the Neuropathologic Laboratory of the Philadelphia General Hospital, the author has found 4 instances of primary or metastatic tumor involving the Gasserian ganglion in the records of almost 5000 cases. These records are composed largely of the neuropathologic findings at autopsy in various types of cases in which disease of the nervous system had been suspected during life, and a small percentage of reports based upon the findings in biopsy material obtained at operation.

Case Reports.‡ Case 1 (Univ. Hosp., Surg. No. 11516 and No. 12069).—C. P. C., a male, aged 47 years, was admitted to the service of Dr.

* Based on material from the Neurologic, Neurosurgical and Neuropathologic Departments of the Hospital of the University of Pennsylvania, and the Neurologic, Radiologic and Neuropathologic Departments of the Philadelphia General Hospital.

† Read in abstract at a meeting of the Philadelphia Neurological Society, February 26, 1932.

‡ Drs. William G. Spiller, Charles H. Frazier, J. B. Carnett, B. J. Alpers, F. C. Grant and N. W. Winkelman have kindly given the author access to the records and material in their respective departments for the purpose of this report. The cases described herein are taken, as indicated, from these sources.

Frazier on August 16, 1927, complaining of pain in the left side of the face. The onset had been with pain in an upper left premolar tooth 13 months previously. It had increased in extent until at the time the patient came under observation, it involved the entire left trigeminal distribution. The pain was almost constant, but there also occurred acute paroxysms of tic-like pain 3 or 4 times daily. The patient had had the left infraorbital nerve sectioned previously, and there was some hypesthesia of the face which was supposed to be the result of this operation. The motor branch of the trigeminus was unaffected and the cornea was not anesthetic. There was some defect of hearing in the left ear which was attributed to a chronic otitis media. The examination was otherwise negative.

Dr. F. C. Grant surgically exposed the Gasserian ganglion. A discrete tumor of the ganglion, probably involving the 7th cranial nerve also, and eroding the petrous portion of the temporal bone, was found and removed. The excised tumor mass measured 2 cm. by 1.5 cm. by 0.5 cm. Dr. Winkelman reported that it showed, microscopically, remnants of what was probably Gasserian ganglion here and there, with much-altered ganglion cells. The entire section was overrun with connective tissue, with areas of calcification scattered throughout. The tissue was very cellular with numerous small round nuclei. Most of the cells were not unlike lymphocytes in appearance; others had irregular elongated nuclei, definitely young connective-tissue elements. Scattered throughout the tissue were small islands of cells with large vesicular nuclei containing faint chromatin granules.

Microscopically, Dr. Winkelman stated, "the nature of these abnormal cells, most of which are arranged in islands, is doubtful. They are probably identical with the capsule cells of the ganglionic elements and superficially resemble endothelial elements, even though they are in all probability ectodermic in origin. There has been a recent tendency to label tumors of this sort 'Schwannomas' or sheath neuromas. There are present here also cells of a chronic inflammatory nature, such as have been described in other tumors of this sort."

At the time of discharge there was some residual pain referred to the left cheek and the mouth, described by the patient as deep "bone pain," and there was left 7th nerve palsy.

About 4 weeks later, a difficulty in swallowing and an impairment of speech had developed, and the pain had become much worse again and had spread from the face to the occiput. Enlarged submaxillary lymphatic nodes had appeared by the time he was seen again, 7 weeks after the operation, and at that time there was complete left 5th, 7th, 9th, 10th and 12th nerve palsy, and partial bilateral 8th nerve involvement, more on the left side. A roentgenogram showed some atrophy of the dorsum sellæ. Dr. Grant then exposed and removed a tumor in the posterior fossa, situated directly over the posterior lacerated foramen. The tumor measured 1 cm. by 5 mm. by 7 mm. and showed the same microscopic structure as the tumor of the Gasserian ganglion. Death occurred Nov. 17, 1927.

Case 2* (Univ. Hosp., Neurol. No. 71898; Surg. No. 3089).—W. M., a male, aged 34 years, was admitted to the service of Dr. Spiller on February 19, 1924, complaining of headache, numbness of the left side of the face, and weakness of the lower extremities. The onset had been with headache, vertigo, pain in the left side of the face and impairment of vision about simultaneously 1 year before admission. For 6 months he had been subject to occasional transient fainting attacks, and during the period of observation a Jacksonian attack affecting the right arm and leg occurred. There

* This case was reported by Dr. F. C. Grant at the meeting of the Philadelphia Neurological Society of May 25, 1924. As his report was not published in the Society Transactions, he has kindly permitted the author to include the case in this communication.

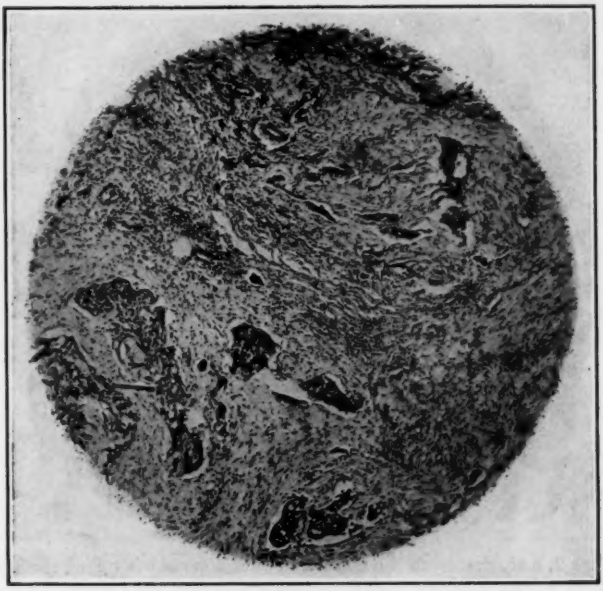

FIG. 1.—Section of the Gasserian ganglion of Case 1, showing the fibrosis, the inflammatory cell infiltration, and the nests of tumor cells.

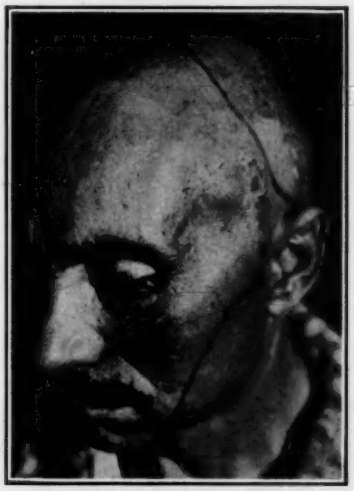

FIG. 2.—Photograph of the patient (Case 1) showing the borders of the postoperative area of anesthesia in the trigeminal distribution marked by ink lines

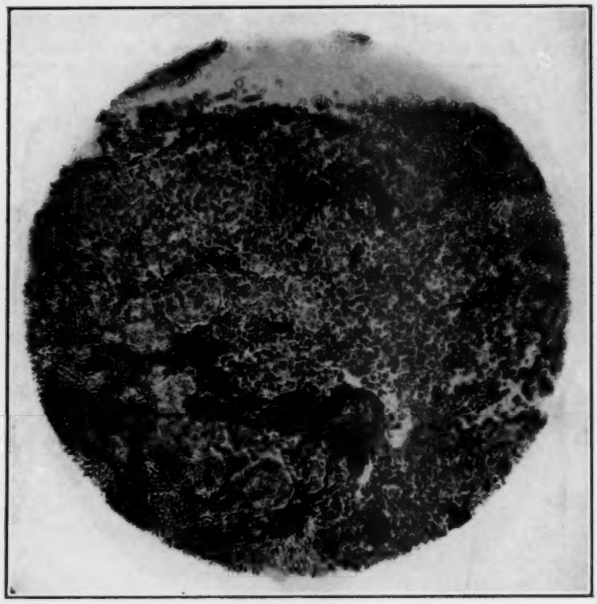

FIG. 3.—Case 2, a section from the Gasserian ganglion showing the primitive type of cells, many of which are arranged in globular groups.

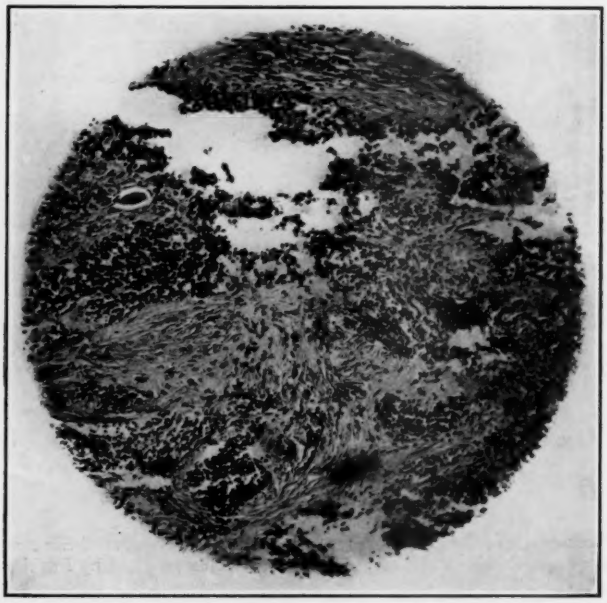

FIG. 4.—Case, 3, a section from the Gasserian ganglion showing the dense fibrous background, the inflammatory reaction, and the islands of tumor cells which have the appearance of young fibroblasts.

was a history of a luetic infection at the age of 23. The examination showed a hyperalgesia of the left forehead and cheek, a diminution of the recognition of touch on part of the left forehead, but not on the cheek, and a diminution of the left scleroconjunctival reflex. The lachrymal reflex was distinct. At times there was a slight impairment of pain and temperature sensation in part of the distribution of the first division of the left trigeminus. There was slight ocular sympathetic involvement on the left. The left masseter and temporal muscles were weak and there was slight weakness, peripheral in type, of the left side of the face. A Bárány examination by Dr. L. Fisher gave findings very suggestive of a left cerebellopontile angle lesion. The tendon reflexes were hyperactive, more so on the right side, and there was abortive ankle clonus on the right. The blood Wassermann was positive.

Dr. Grant exposed the left Gasserian ganglion and found and removed a tumor of the ganglion. He thought at that time that the growth involved the posterior fossa as well, since neoplastic tissue apparently accompanied the sensory root.

Dr. J. McFarland has reported on the fragments of tissue removed at operation. "The sections are of an embryonal type of tumor of nervous origin representing an early stage of development, containing numerous globes of cells such as characterize the neurocytomas, very closely related to or resembling the equally primitive brain tumor called medulloblastoma. They are malignant both by invasion and by metastasis. The tissue also most closely resembles the retinoblastoma or glioma of the retina." His diagnosis was neurocytoma.

Roentgenologic and antiluetic treatments were carried out subsequently. Eleven months after operation, the patient had some epileptiform attacks. Examination about that time showed an elevation of the optic disks of 1 diopter. Except for an increased degree of mental sluggishness and a complete motor and sensory 5th nerve paralysis on the left, the neurologic examination showed no marked changes over previous examinations. The cerebrospinal fluid Wassermann, which had been negative previously, was then positive. After that time, contact with the patient was lost, and the final outcome is not definitely known.

Case 3 (Univ. Hosp., Surg. No. 22072).—L. C., a male, aged 33 years, was referred to the service of Dr. Frazier by Dr. M. C. Thrush on June 27, 1931. He complained of pain in the right side of the face and blindness in the right eye. The onset had been in November, 1930, with pain in the upper gum. A tooth had been removed for the relief of the pain, but on the same day severe pain in the malar region had developed, and within a month had involved the entire right side of the face and the side of the head. Impairment of vision had begun simultaneously with the onset of the pain and had progressed to complete blindness in the right eye within 3½ months. Prominence of the right eyeball had been noticed 1 month after the onset. The speech had been impaired for a short time before he entered the hospital. An alcohol injection 6 weeks before admission had failed to relieve the pain. There had been some anorexia and occasional vomiting, and he had lost weight, but the duration of these symptoms was uncertain. He described the pain as a "hard, throbbing ache" which was constant and was becoming worse. This pain was limited to the distributions of the second and third divisions of the right trigeminal nerve, but in addition to this there occurred, each afternoon, a bitemporal headache which lasted for 4 or 5 hours.

The general *physical examination* was essentially negative. The patient had a tendency to sleep much of the time, and was not entirely coöperative. The speech was mumbling in character and almost unintelligible. The Romberg was positive, and the gait unsteady. Skilled movements were

poorly executed and there was rather marked adiadochokinesis of the right hand. The motor power was generally reduced without any marked difference on the two sides and with no distinct paralysis of any limb. The tendon reflexes were about normal on the two sides, and there were no pathologic reflexes. The right eye was entirely blind and there was primary optic atrophy on this side. The vision in the left eye was 6/9. There was weakness of the right external rectus muscle, the internal rectus, and possibly a little bilateral ptosis. The right pupil was dilated and reacted sluggishly to light and in convergence. Exophthalmus of the right eye was present.

Hyperesthesia in the right trigeminal distribution was noted, but no loss of sensation could be demonstrated. The corneal reflex was present on each side, but that of the right side may have been a little sluggish. The masseter, temporal and pterygoid muscles were equally innervated. The sense of taste was normal. No demonstrable impairment of function of the other cranial nerves could be demonstrated, although the speech was decidedly thick. The patient was left-handed.

The blood Wassermann test was negative. The cerebrospinal fluid was under pressure of 120 mm. of water, contained 14 cells per c.mm., showed an increased protein content, a negative Wassermann reaction, and a colloidal gold curve of 0001110000.

The roentgenograms showed a normal pituitary fossa. The encephalogram after injection of air indicated that the ventricles were top normal in size. The subcortical markings were almost completely absent on both sides, and a few dilated pathways were seen in the right posterior parietal region. Dr. Kornblum interpreted the findings as indicative of obstruction and dilatation of the pathways in the region of the Island of Reil on both sides, somewhat more marked on the right side.

The patient left the hospital on July 15, 1931, and he declined to return for further observation or treatment. Subsequently, he was admitted to another hospital where apparently an exploratory operation was done, but the tumor was not removed. Death occurred in December, 1931.

Pathologic examination (Dr. B. J. Alpers) was obtained through the courtesy of Dr. E. A. Dougherty. There was an operative incision in the dura over the right frontal lobe. Within the folds of, and under the dura on the inferior and lateral surfaces of the right temporal lobe was a firm dumb-bell shaped tumor involving the Gasserian ganglion, being continuous with the central trigeminal root. Half of the tumor seemed to be enshrouded in two folds of dura, possibly the two folds of Meckel's space. The other half lay under the dura. There was considerable thickening of the tentorium on the left side. Microscopically the tumor was encapsulated, and scattered in its substance were small clusters of degenerated ganglion cells and irregular bundles of nerve fibers surrounded by Schwann cells. In the tumor there was an exceedingly dense background of collagenous and fibrous tissue, through which were scattered islands of tumor cells completely surrounded by fibrous tissue. The cell clusters were solid in some areas, and in others there was central degeneration, resulting in an acinar appearance. The clusters were composed of young fibroblasts, cells with round nuclei of moderate size, occasional polymorphonuclear cells, and fairly numerous cells with fragmented nuclei. It appeared to Dr. Alpers that young fibroblasts were growing from the fibrous walls into the cellular islands. The microscopic diagnosis was fibroblastoma.

Discussion. The diagnosis of tumors of the Gasserian ganglion must be governed by the appearance of such symptoms and signs as have been observed by careful clinicians in other verified cases. The usual symptomatology has been described in detail by many authors, among whom may be mentioned Spiller,[14] Cadwalader,[11,15]

Frazier,[12] Cushing,[13] Sachs,[1] and Peet.[2] Pain in the distribution of the trigeminal nerve of the side of the lesion, usually occurring early in the course of the disease, having a dull and constant quality, sometimes with paroxysms of acute tic-like pain, has been stressed repeatedly. The objective diminution or loss of the sensations of touch, pain, heat and cold in a part or all of the ipsolateral trigeminal distribution is considered common, the combination of spontaneous pain and impairment of sensation objectively (anesthesia dolorosa) being regarded by many as diagnostic of tumor in the absence of syphilitic or tuberculous infection. Diminution of the scleroconjunctival reflex on the same side, loss of the lachrymal reflex and the gag reflex, impairment of taste on the anterior part of the tongue, and impairment of function of the motor branch of the trigeminus and of the nerves supplying the intrinsic and extrinsic muscles of the eye are not unusual. With the extension of the growth to invade or compress the cerebral tissue or the structures of the posterior fossa, additional symptoms and signs occur, dependent upon the structures affected.

That the diagnostic criteria usually emphasized do not occur in every case of tumor of the Gasserian ganglion was suggested, however, by the indistinctness of the signs in Cases 1 and 3 and by the fact that Hellsten's[16] review of the literature in 1914 and Frazier's[12] analysis of 29 cases in the literature up to 1918 indicated that the occurrence of symptoms and signs definitely referable to neoplastic disease of the ganglion had not been observed as frequently as one would expect. Consequently, the author analyzed the available recent case reports, together with some of the earlier ones in which detailed studies had been recorded, in order to determine the clinical findings and the results of treatment in a more uniformly studied series. For the purpose of this analysis only verified cases of tumor arising in the ganglion or its immediately adjacent sheaths, and such secondary tumors as had invaded the nervous tissues only in the immediate neighborhood of the ganglion were included. The cases of Peet[2] and of Woltman[17] were omitted from the statistical study because of the probable involvement of the peripheral branches of the trigeminus prior to actual ganglion invasion.

The more important features described in the reports included in this study are summarized in Table 1. Under the heading of "Initial Symptoms" are listed those manifestations which occurred first in the course of the disease or so soon after the onset as to make them practically indistinguishable from the first symptom. Under "Objective Findings" are listed the important neurologic signs observed in the study of the patients and ascribed to the effects of the tumors.

A more detailed analysis of these 22 cases (Table 2) gives the frequency of occurrence of the various manifestations.

TABLE 1.

Author.	Reference.	Initial symptoms				Objective findings.						
		5th nerve pain.	5th nerve numbness.	5th motor weakness.	Other symptoms.	Sensory loss (5th).	Motor weakness (5th).	Hyperesthesia (5th).	Impaired reflexes (5th).	Impaired taste.	Sympathetic signs.	Signs not related to 5th nerve disease.
Spiller, Case 1	14	+	..	+	..	+	+	..	+	+	..	+
Spiller, Case 2	14	+	..	..	..	..	+	+	..	..	+	+
Plummer and New	18	+	..	..	+	+	+	..	+	+	..	+
Sachs	1	+	..	..	+	..	+	..	..	..	..	+
Percy	19	+	..	..	..	+	?	..	..	..	?	+
Cadwalader	11	+	..	..	..	+	+	..	+	..	..	+
Cushing, Case 328	13	..	..	..	+	+	+	..	..	..	..	+
Shelden, Case 1	20	+	..	..	..	+	+	..	+	+	+	+
Shelden, Case 2	20	?	..	..	?	+	+	..	..	..	?	+
Shelden, Case 3	20	+	..	..	..	..	+	+	..	..	..	+
Parker, Case 4	3	+	+	..	..	+	+	..	+	..	..	+
Rand	5	+	..	..	+	+	?	+	..	..	..	+
Russell, Case 1	4	..	+	..	+	+	..	..	..	..	..	+
Russell, Case 2	4	+	..	..	..	..	..	..	..	..	..	..
Altmann, Case 1	6	..	..	..	+	+	..	..	+	..	..	+
Altmann, Case 2	6	..	..	..	+	+	..	..	+	..	..	+
Gaines, Case 2	7	+	..	..	+	+	+	..	+	..	..	+
Learmonth and Kernohan	8	+	..	..	..	+	+	..	+	+	..	+
Cooper	10	+	..	..	..	+	..	..	..	..	..	+
Case 1 of this report	..	+	..	..	..	?	..	..	..	..	..	+
Case 2	..	+	+	..	+	+	+	+	+	..	+	+
Case 3	..	+	..	..	+	..	..	+	?	..	..	+
Totals	..	17+	3	1	10+	16+	13+	5	10+	4	3+	21

TABLE 2.—ANALYSIS OF 22 CASES.

Initial Symptoms:

Pain in the ipsolateral trigeminal distribution	17 times
Ipsolateral trigeminal pain (possibly not initial)	1 time
Ipsolateral numbness in trigeminal distribution	3 times
Ipsolateral trigeminal motor weakness	1 time
Impairment of vision	4 times
Nausea, vertigo, tinnitus or impaired hearing	4 times
Headache	3 times
Diplopia or ptosis	2 times
Cervical lymph node enlargement	2 times
Paresis of extremities	1 time

Objective Findings:

Impairment or loss of touch, pain, heat or cold sensations in ipsolateral trigeminal distribution	16 times
Trigeminal sensory impairment of doubtful etiology	1 time
Ipsolateral trigeminal motor weakness	13 times
Questionable ipsolateral trigeminal motor weakness	2 times
Hyperesthesia or hyperalgesia in ipsolateral trigeminal distribution	5 times
Diminution or loss of ipsolateral conjunctival reflex	10 times
Ipsolateral impairment of taste on anterior part of tongue	4 times
Diminution of ipsolateral lachrymal reflex	1 time
Ipsolateral impairment of sympathetic function	3 times
Questionable sympathetic impairment	2 times

Objective Findings Referred to Other Cranial Nerves:

Ipsolateral 3d, 4th, or 6th nerve involvement	15 times
Ipsolateral 8th nerve involvement	9 times
Ipsolateral impairment of hearing (doubtful etiology)	4 times
Ipsolateral 7th nerve involvement	8 times
Ipsolateral 9th or 10th nerve involvement	4 times
Questionable 9th or 10th nerve involvement	1 time
Ipsolateral 12th nerve involvement	4 times

Other Signs:

Enlargement of cervical lymph nodes	6 times
Ipsolateral exophthalmus	4 times

Although such an analysis as this, based upon reports by different observers whose findings necessarily were subject to individual variations, cannot be precise and all-inclusive, nevertheless it gives reasonable assurance that no single symptom or sign occurs invariably. In 3 cases (Cushing,[13] and Altmann's[6] 2 cases) the initial symptoms had no suggestion of trigeminal disease; and in another (Shelden's[20] Case 2) tinnitus of undetermined cause preceded the 5th nerve symptoms by 1½ years. In 2 instances (Sachs'[1] case, and Russell's[4] Case 2) no objective disturbance of the 5th nerve sensory function could be found; and in 2 others (Cases 1 and 3, of this communication) the only objective disturbances of the trigeminal functions were, respectively, some hypesthesia in the area of a previous peripheral nerve avulsion, in Case 1, and hyperesthesia in the trigeminal area in Case 3. The author has had the privilege of reviewing the history and of examining the sections of the ganglion of another case reported by Carnett[21] in which there were metastatic carcinomatous deposits scattered widely throughout the bones and the organs, one deposit having invaded the left ganglion. Although there were definite nests of carcinomatous cells in the ganglion itself, the only objective clinical findings which might have been dependent upon such a lesion were a decrease in size of the left pupil as compared to the right and a tenderness of the scalp and face to pressure. The only suggestive symptoms in the history were headache and the statement of the patient that food did not taste good to him. That distinct objective changes had not occurred in these cases is remarkable when it is noted that at the time of observation symptoms had been present in Russell's Case 2 for 17 months, in Sachs' case for 10 months, in the author's Case 1 for 13 months, and in Case 3 for 7 months.

These exceptional cases have been mentioned particularly in order to illustrate the difficulties encountered in arriving at a diagnosis in some instances. Of the 22 case reports analyzed, the majority were sufficiently clear-cut to justify a positive diagnosis, and in these latter no essential variations from the usual clinical picture were encountered. With the exception of the cases particularly mentioned above, some impairment of the sensory or motor functions or of the reflex arcs dependent upon the integrity of the trigeminal pathways had given the clue pointing toward a destructive lesion of these pathways.

So far as the manifestations relating to the Gasserian ganglion *per se* are concerned, therefore, the clinical picture as formulated on the basis of the available reports of recent date most frequently is characterized either by an initial symptom such as pain in some part of the trigeminal distribution, subjective numbness in that area, impairment of vision or hearing, nausea, vertigo, or headache; or by an objective finding such as trigeminal sensory impairment or hyperesthesia, diminution of the corneal reflex, or weakness of the motor division; or by a combination of more than one of these

manifestations. It should be emphasized again, however, that occasional cases apparently have had no subjective symptoms pointing to the ganglion, and that a few others have showed no definite objective evidence of disease of the ganglion or the motor division. In conformity with the views of former writers, this study indicates that in the clinical course of ganglion tumors other cranial nerves on the side of the lesion, particularly the nerves to the ocular muscles, the 8th, the 7th, the 9th and 10th, and the 12th, in that order of frequency, may be affected.

The value of roentgenology in diagnosis does not appear to be dependable. Partial destruction of the sella turcica or erosion of the base of the skull were noted in 3 of the analyzed cases, but the changes were not distinctive of ganglion tumor. In the author's Case 3, the encephalogram was suggestive but not conclusive.

Syndromes closely resembling the clinical picture of tumor of the Gasserian ganglion may occur in association with tic douloureux, neuralgias secondary to sinus or dental disease, atypical neuralgia, postzoster neuralgia, syphilis, tuberculosis and cerebellopontile angle tumor. For discussions of these conditions and the helpful differential points, the reader is referred to the communications of Parker,[3] Frazier,[12,22] Cushing,[13] Mixter and White,[23] Potts,[24] Cadwalader,[15,25] Spiller and Camp,[26] and Spiller and Potts.[27] That cerebellopontile angle tumor occasionally may produce a symptom complex indistinguishable from that caused by a tumor primary in the Gasserian ganglion has been demonstrated in the experiences of Weisenburg,[28] Parker,[29] Oppenheim,[30] of Krause and of Lexer (quoted by Cushing[13]).

Contemporary opinion as to the pathology of tumors arising in the region of the ganglion varies to such an extent that the question cannot be considered in detail here. Spiller's[14] warning of many years ago against the rigid classification and differentiation of such tumors on the basis of the interpretations of different observers applies today. The degree of malignancy of the tumors in this region, whether they be primary or metastatic, obviously influences the prognosis. However, a more definite and clear-cut microscopic classification, as well as further data on the clinical course of patients in whom these tumors are demonstrated is necessary before different plans of treatment dependent upon the pathology can be formulated. The pathologic diagnoses reported by the authors in the 22 cases analyzed for this communication were as follows: Endotheliomas, 10; neuromas, 2; sheath neuromas, 2; neurocytoma, 1; neurofibrosarcoma, 1; sarcoma, 1; fibroblastoma, 1; chondroma, 1; neurofibroma, 1; undetermined, 2.

Although surgical treatment of tumors of the Gasserian ganglion has been practised since the time of Krogius'[31] first operation on such a case, the results of surgical treatment had not been encouraging until the time of Frazier's[12] case. Of the cases which the author has reviewed, 17 had been subjected to operations for removal of

the tumor or section of the sensory root of the trigeminus, decompressive operations had been done on 2 others and apparently an exploratory operation on a 3d case. Postoperative relief of pain resulted in 12 of the operated cases, the degree of relief and of permanence of relief varying considerably. Of the operated cases in which follow-up notes were mentioned and in which partial or total extirpation of the tumor or section of the sensory root had been done, the average period of known relief was 4.7 months and the average known duration of life after operation was 7.5 months. These averages are conservative, as 7 of the patients were living when last heard from, the periods of relief or the duration of life in these cases being counted as corresponding with the interval between operation and the date of the last follow-up note. The return of spontaneous pain after surgical extirpation of the tumor and division of the sensory root may be accounted for by recurrence of the tumor or invasion of the posterior fossa, as in Case 1. Following operation, irradiation is given and has been of value, as illustrated by the results in Rand's[5] case.

The effect of operation upon the duration of life cannot be determined until larger groups of operated cases have been studied. However, it may be pointed out that in this series of 20 operated cases, death attributable to operation occurred only 2 times, the operation having been done for the purpose of decompression in 1 of these cases and for exploration in the other.

Sachs'[1] recommendation that operation be performed on patients having severe continuous pain in the trigeminal distribution, in the absence of sinus disease, without awaiting involvement of the motor branch of the trigeminus, appears to be justified by the results of surgical treatment in this group of cases. Furthermore, it may be pointed out that a ganglion tumor occasionally may be present for a considerable time without giving rise to any of the usual objective signs. In view of these facts, and in the light of Frazier's[32] low operative mortality of 0.26 per cent from the middle fossa operation for trigeminal neuralgia, the justification for early middle fossa exploration by a competent operator for patients suffering unexplained constant trigeminal pain, with or without typical objective manifestations, does not appear to be strained. The relief of pain alone by section of the sensory root in otherwise inoperable cases, as previously suggested by Frazier,[33] may make the middle fossa operation worth while for such cases.

Summary. Three cases of tumor primary in the region of the Gasserian ganglion are reported. A review of 19 additional cases in the literature is summarized to illustrate the frequency of occurrence of the various initial symptoms and of the objective manifestations, and the results of operation in such cases. The difficulties of diagnosis in some instances are pointed out. The principal conditions which are to be differentiated from tumor and occasional indistinguishable conditions are mentioned. Attention is directed

to the gratifying results in a few cases subjected to early operation; to the relatively low operative mortality in excision of early lesions and in the less hazardous procedure of section of the sensory root; and to the possibility of symptomatic relief by division of the sensory root in cases of inoperable tumor.

Conclusions. 1. The clinical diagnosis of tumor of the Gasserian ganglion is not always possible in the light of our present knowledge, even when definite neoplastic involvement of the ganglion has occurred.

2. Occasionally such conditions as tic douloureux, atypical neuralgia, postzoster neuralgia, syphilis, and rarely tuberculosis and angle tumor may produce a clinical picture which cannot be distinguished from early tumor of the Gasserian ganglion.

3. Exploratory operation in the region of the Gasserian ganglion by competent operators is justified for patients who suffer suspicious constant trigeminal pain not satisfactorily explained, and for patients who show objective indications of interruptions of the trigeminal motor or sensory pathways without evidence of an etiology other than ganglion tumor.

4. Palliative section of the sensory root is justified in patients in whom extirpation of the tumor is not feasible.

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PNEUMONIA IN KEROSENE POISONING.

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The toxic properties of kerosene are generally recognized, but the way in which the oil exerts its harmful effect in cases of serious or fatal poisoning is not clearly stated in the literature. Among the 23 cases admitted to the Roper Hospital in the past few years there have been a number of severe manifestations and 2 deaths. Many other children have been treated in the emergency room and allowed to return home because their symptoms were slight. Cases seem to be more common than previously and, because of the probability of the occurrence of serious intoxications in the future, the recent cases have been reviewed and certain experiments undertaken in an attempt to clarify the subject.

In the children made ill by kerosene the chief signs have been marked drowsiness or actual coma, fever and abdominal tenseness. Cyanosis and convulsions have been present in 2, vomiting and diarrhea in 2, and acetonuria in 7 instances. Nine children have developed definite signs of pulmonary involvement varying from mild bronchitis to severe and fatal pneumonia.

The more noteworthy cases were as follows:

Clinical Notes. Case 1.—Colored, male, aged 1 year. Drank a "small amount" of kerosene, and about 1½ hours later became comatose, whereupon he was brought to the hospital and given a gastric lavage. Fine and coarse râles were heard over both lungs and dullness was found over the bases. A roentgenogram showed clouding of nearly the whole of the left lung and of an area in the right base. In spite of supportive treatment, after rousing somewhat, this child lapsed into coma and died about 11 hours after the ingestion of the kerosene (Fig. 1).

Case 2.—Colored, female, aged 14 months. Swallowed about half a glass of kerosene and had gastric lavage within about 20 minutes. She was coughing, comatose and cyanotic, had contracted pupils, coarse râles over both lungs and showed a fine, almost constant generalized twitching. A colonic irrigation yielded fluid with a strong odor of kerosene. A roentgenogram made 3½ hours after the kerosene was taken showed areas of increased density over both lungs along the course of the larger bronchi. Death occurred about an hour later.

Case 3.—White, female, aged 3 years. Drank an undetermined amount of kerosene and almost immediately choked, became cyanotic and rapidly became drowsy. Gastric lavage was done within 20 minutes. Coarse râles were heard over both lungs, and a roentgenogram showed bilateral mottling. Later in the day high pitched breath sounds and crackling râles were heard in the left base. Next day the signs were less marked, although the roentgenogram showed practically the same picture. Three days later the lungs were clear clinically, and uneventful recovery followed. The edge of this

child's liver was 3 cm. below the costal margin, but no connection between this enlargement and the current illness was found.

CASE 4.—Colored, male, aged 2 years. Drank kerosene and was given castor oil and salts before he became comatose. His stomach was washed after about 2½ hours. Râles, dullness and tubular breathing were found at the angle of the left scapula, and a roentgenogram showed clouding of the left lower lobe. Six days later the picture showed less density. After 8 days dullness was still present, but the child was so much improved that he was discharged (Fig. 3). A roentgenogram taken 8 months afterward was negative.

CASE 5.—White, male, aged 2 years. Took "three swallows" of kerosene, cried, flushed, coughed and soon became drowsy. His stomach was washed in about 2 hours' time. Occasional coarse râles were heard over both bases; the roentgenogram was negative. By the following day he was ready for discharge.

CASE 6.—White, female, aged 2 years. Drank kerosene, but was not seen at the hospital until 2 days later, when she showed râles and diminished resonance on both sides, and a tense abdomen. Recovery followed in 7 days.

CASE 7.—White, female, aged 2 years. Drank kerosene. Seen 5 days later and had cough, fever, pain in chest and a few râles. Three days later she seemed entirely well.

CASE 8.—White, female, aged 32 months. Drank about 3 ounces of kerosene. Developed no marked symptoms. Recovered.

CASE 9.—Colored, male, aged 3 years. Drank a half glass of kerosene. Had gastric lavage within a half hour. He developed a temperature of 104° F. and showed râles over both bases and roentgenologic evidence of congestion in those areas. He recovered in 24 hours.

CASE 10.—Colored, male, aged 14 months. Had gastric lavage 10 minutes after drinking kerosene. He showed râles in both bases, and the roentgenogram showed clouding in the lower half of both lungs. Three days later the râles had disappeared, but the film was essentially the same. This child did not appear very ill and seemed well within 24 hours after the onset. The stool showed no blood.

The laboratory findings were not particularly significant. An increased total leukocyte count and polymorphonuclear percentage were usual. Methemoglobin was not demonstrated in the 4 cases in which tests were made. The cholesterol content of the blood was apparently reduced.

Usually the respiration was rapid, going as high as 140 in Case 1. The pulse rates were likewise high. In Case 3 the rectal temperature reached 104.6° F., in Case 9 it reached 104° F., and in Case 10 it went to 102.6° F., but did not exceed 102° F. in the others, and was of short duration as a rule. Cyanosis did not persist in the children who recovered.

In an effort to discover characteristic changes caused by kerosene, a few experiments with dogs were made. The clinical changes produced were quite similar to those found in the children.

Animal Experiments. DOG 1 (Weight, 14 kg.).—Was given morphin sulphate, ¼ gr. and atropin sulphate, $\frac{1}{150}$ gr., at 9.50 A.M. At 10.30 A.M. blood was taken for examination and 10 minutes later 250 cc. kerosene were given by stomach tube. At 11 A.M. the dog was drowsy. Rectal temperature at that time was 38° C., at 5 P.M. it was 40° C., and at 8 P.M., 38° C. The

FIG. 1.—Case 1. Lungs 3 hours after kerosene was taken.

FIG. 2.—Case 3. Lungs 3½ hours after kerosene was taken.

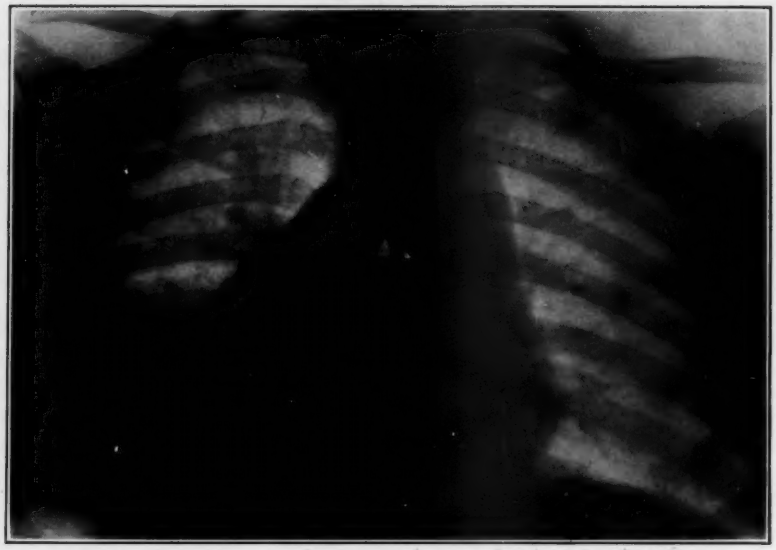

FIG. 3.—Case 4. Lungs about 5 hours after kerosene was taken.

FIG. 4.—Lungs of dog after intratracheal injection of kerosene. (Experiment IV.)

dog showed no other signs of intoxication and next day appeared well. Kerosene was passed per rectum on this second day. A roentgenogram of the chest 23 hours after kerosene was given was negative. A second sample of blood was taken 2½ hours after the first bleeding.

TABLE 1.—RESULTS OF BLOOD EXAMINATIONS.

	Before kerosene.	2 hrs. after kerosene.		Before kerosene.	2 hrs. after kerosene.
Hemoglobin (Dare)	80	78	R. B. C. (millions)	5.5	5.5
Sugar	65.8	63.9	Leukocytes	9700	12,500
Urea	7.8	8.3	Lymphocytes	33	26
Chlorids	546	528	Polymorphonuclears	62	71
Creatinin	1.3	1.0	Mononuclears	1	2
Cholesterol	54.7	44.0	Basophils	2	0
CO_2	64	56	Eosinophils	2	1

These figures parallel the findings in the children, showing a moderate increase in leukocytes, polymorphonuclear percentage and a lowering of the cholesterol value.

DOG 2 (Weight, 6 kg.).—After administration of morphin and atropin was given 100 cc. of kerosene by stomach tube. Three hours later he was drowsy and his pupils were dilated, but otherwise showed no ill effects. Carbon dioxid combining-power was 57 before the kerosene was given, and 62 after 3 hours.

DOG 3.—Was given 100 cc. of kerosene by stomach tube. He vomited about 35 cc. Hemoglobin before administration was 105, and 2½ hours later was the same.

DOG 4.—A bitch, weighing 4.7 kg., showed a negative roentgenogram of the chest. Under light ether anesthesia 5 cc. of kerosene were injected into the larynx with the aid of a laryngoscope. Almost immediately there were convulsive twitchings of the body. One-half hour later the respiration was 180, rectal temperature, 39° C. After an hour, except for rapid respiration, the animal seemed to be recovering well. A roentgenogram showed a heavy shadow in the right lower lobe. After 24 hours the shadow in the right lower lobe was still present. The animal recovered uneventfully.

The similarity between the shadow in Case 4 and in the injected animal may be noted by comparison of the roentgenograms (Figs. 3 and 4).

DOG 5 (Weight, 12 kg.).—Was given 200 cc. of kerosene by tube. Through error the tube entered the larynx, as shown later at autopsy by the presence of a large amount of kerosene in the lungs. The effect was immediate; the dog developed marked extensor rigidity with opisthotonos, urinated, vomited (or coughed out) a few cubic centimeters of kerosene, rapidly became comatose, with Cheyne-Stokes respiration, and died in 45 minutes. The rapid development of symptoms in Case 2 suggests that the child might have aspirated a large amount of kerosene and followed a course similar to that produced by the rapid entrance of kerosene into the lungs of the dog.

DOG 6 (Weight, 14.85 kg.).—Without preliminary anesthesia he had 10 cc. of kerosene injected into the trachea through the neck at 9 P.M. At 9.15 P.M. he showed marked dyspnea and ataxia. At 9.25 P.M. he was unable to stand, and very dyspneic. His rectal temperature fell from 38° to 37.5° C. Respiration was 116 per minute. At 9.40 he was very drowsy, with irregular respiration, but could be roused. At 12 P.M. his temperature had dropped to 35.5° C., respiration to 64. He died between 1 A.M. and 8 A.M.

Autopsy showed both lungs congested, with excess of fluid, and consolidation of the left lower lobe and relative consolidation in the right lower and parts of the left upper. Microscopically capillary engorgement and heavy edema were present. In the more solidified parts the alveoli were

filled with fibrin and fluid, with large infiltration by small cells, some polymorphonuclears, but most of the lymphocyte type, obscuring alveolar walls and more or less filling alveoli and small bronchioles.*

TABLE 2.—BLOOD FINDINGS IN 10 CASES OF KEROSENE POISONING.

Case.	Leukocytes (thousands).	Lymphocytes.	Polymorphonucleears.	Monocytes.	Basophils.	Eosinophils.	Hemoglobin (per cent).	Sugar (mg. per 100 cc.).	Urea.	Creatinin.	Blood chlorids.	CO_2.	Cholesterol.	Methemoglobin.
1	19.3	24	72	2	1	1	70	...	....	...	...	66	....	0
2	18.4	30	65	1	0	4	70	126	11.3	1.3	...	64	47.6	0
3	13.5	46	51	1	0	2	68	105	8.9	1	511	66	41.2	0
4	10.1	25	69	4	0	2	..	118	17	...	...	50		
5	11.1	19	81	0	0	0	70	84	10	...	396	69		
6	23.4	26	68.5	3	1.5	1								
7														
8	18.5	27	72	1	0	0	85	67	9.5	1.2	475	82	64.5	0
9	11.1	35	54	6	0	5	60							
10	12.5	39	57	3	0	1	75							

TABLE 3.—URINE IN 10 CASES OF KEROSENE POISONING.

Case.	Reaction.	Albumin.	Sugar.	Acetone.	Casts.	Pus.	Blood.
1	Acid	++	0	0	0	0	0
2							
3	Alk.	+	0	Trace	0	+	0
4	Acid	0	0	0	0	0	0
5	Acid	0	0	0	0	0	0
6	Acid	0	0	++	0	0	0
7							
8	Acid	+	0	0	0	++	0
9	Acid	0	0	0	0	0	0
10	Alk.	0	+	++	0	0	+

DOG 7 (Weight, 6.15 kg.).—Had 7 cc. of kerosene injected into his trachea. He developed symptoms very similar to those noted in the last experiment, and died within 2 hours. *Autopsy:* Congestion, edema, hemorrhage. Early pneumonia, cellular exudation—not prominent as in other dog and proportionately more polymorphonuclears. Kidney: granular swelling of epithelium of convoluted tubules; fragmentation, granularity, vacuolization of epithelium of Henle's loop and collecting tubules. Liver: cells of central lobular zones quite granular. Trachea: minor desquamation of epithelium, a submucosal hemorrhage. Lungs: vascular engorgement, alveoli practically filled with blood, hyalin coagulum and cells, predominantly lymphocytes, next in prominence mononuclears, but a goodly proportion of neutrophils; small areas of necrosis here and there, with leukocytic accumulation.*

* Autopsy by Dr. K. M. Lynch. A more detailed report of the pathologic findings will be made in another article.

Discussion. The scanty literature relating to kerosene poisoning has little to say regarding the pulmonary complications, and deals mostly with gastrointestinal irritation. The toxic effect of inhalation of the vapor is recognized,[1,2] but no stress is put on the likelihood of aspiration of the oil into the lungs, and the consequent rapid damage to the lung tissue. According to reports, the dose required for poisonous action seems to vary considerably with individuals, and the time for development of coma or serious symptoms likewise appears to be variable. Recovery of an adult after drinking ¾ liter is reported,[3] while a child aged 18 months succumbed to 2 ounces.[4] Death from bronchopneumonia occurred in an infant aged 6 months, into whose mouth an ounce of "petrol" had been poured 1¼ hours before.[3] (Gasoline and kerosene are similar in general composition and effect, except that kerosene is said to be the more reactive.[5]) Seven fatal cases in children are found in detail in the literature.[3,4,6,7,8]

Administration of petrol by stomach tube to rabbits is said by Le Gludie and Turlais[3] to produce pulmonary congestion and punctate hemorrhage. These observers found that as much as 20 cc. per kg. was necessary for toxic effect on the rabbit, and were able to produce only gastrointestinal irritation in dogs.

The development of areas of pneumonic consolidation following the administration of oils by the nose or throat has been demonstrated by Laughlin.[9] Pinkerton[10] also has pointed out the fact that mineral oil evokes a tremendous cellular reaction in the lung, that it is easily emulsified and taken up rapidly by phagocytic cells. He furthermore notes[11] that aspiration of regurgitated stomach contents is not uncommon, and that spasm of the cardia may allow fluid to well back in the esophagus and spill over into the larynx. The type of oil seems to be important in the production of changes in the lungs, for lipiodol (iodized poppy-seed oil) does not cause pneumonia in dogs[12] and is given to human beings apparently without ill effect.

With these considerations in mind, and in view of the clinical and experimental findings, it would seem likely that the pulmonary complications of kerosene poisoning are due to aspiration of some of the kerosene directly into the lungs, or the aspiration of regurgitated kerosene from the stomach, and that the serious and fatal intoxications with this substance are due to the development of pulmonary inflammation with edema and, perhaps, to rapid absorption of the oil from the lungs.

Treatment. The results of treatment are not the most satisfactory. Supportive measures, especially stimulation with caffein, have been used. Colonic irrigations and gastric lavage have been given, but if regurgitation is to be avoided, the use of lavage might be questioned. In 2 cases which recovered, postural drainage was instituted but no direct evidence of its efficacy was noted. The blood

chemical studies have not indicated any line of treatment. Because some of the children showed acetone in the urine, glucose has been given to the cases seen recently.

Summary. Nine cases of kerosene poisoning with pulmonary complications are reported. Leukocytosis with an increased polymorphonuclear percentage has been characteristic. The blood cholesterol appears to be reduced, but no other chemical change is noted. Animal experiments tend to confirm the clinical opinion that the serious and fatal cases of kerosene poisoning are due to the aspiration of kerosene into the lungs, with production of inflammation and edema, and a potentially fatal pneumonitis.

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THE EFFECT OF CEMENT DUST UPON WORKERS.*

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The greater part of the material presented in this paper was gathered from experience met with in assisting in a study of workers who were exposed to varying concentrations of cement dust and from the report of this study, which includes analyses of all the data obtained from dust counts, chemical and petrographic analyses of the dust, morbidity records, and general physical examinations.[1] The purpose of the study was primarily to measure in terms of physical condition and disabling sickness the effects upon the

* Read before the Sixth International Congress on Industrial Diseases in Geneva, August, 1931.

workers of exposure to known quantities of dusts. The study was conducted in a plant which was selected because, in the first place, it appeared to be dusty enough to afford observation of the effect upon health of exposure to large amounts of calcium dusts (regarded by many as possessing properties beneficial to health) and of silica (known to be harmful in its free, crystalline state), and in the second place, the managers of the plant offered to coöperate and assist in the collection of data needed for such a study.

The importance of knowing the effect of cement dust upon workers is obvious, since there are in the United States at least 150 cement manufacturing plants in operation at the present time, employing over 42,000 workers, and a still larger number of persons will be required in the future to meet the increasing demands for cement in road making and building construction and the many new uses to which this product will be applied.

The study was conducted throughout a period of nearly 3 years, and the greater number of the workers underwent two general physical examinations. In addition to the general examinations, persons suspected of having chronic respiratory disease were given special chest examinations, in order to make possible more definite diagnoses. Roentgen-ray films were taken of the chests of employees in different occupations of the industry. The number of dust particles per cubic foot of air was determined for the different parts of the plant where the employees worked. The dust was examined chemically and petrographically. A record was kept also of all absences from work, and those lasting 2 days or longer were investigated by a nurse in the employ of the cement company. If the absence was found to be due to illness, a diagnosis was obtained, if possible, from the attending physician; otherwise, from the symptoms described by the patient.

The manufacturing of American Portland cement requires the mixture of limestone or marl with clay or shale, which are usually obtained by steam-shovelling in open quarries and subsequent crushing by machinery—processes which require little manual labor and hence the number thereby exposed to dust is small. These minerals are mixed in proper proportions and are pulverized by machinery to a fineness of 90 to 95 per cent, passing a No. 100 mesh screen. They constitute the "raw" material prepared outside the plant proper and conveyed automatically into the mill. The dust counts in the crushing and mixing rooms in a plant studied by us are given in Table 2.

The chief constituents of the dust in the crusher houses of the quarry are calcium carbonate, silica, and silicates. The quarry dust is practically 100 per cent inorganic material and contains moisture in amounts which vary in proportion to the amount of moisture in the outdoor air. The proportion of free silica (in the form of quartz) in samples taken from the crusher house, the raw

mill, and the stone house was found to be about the same (by petrographic analysis)—namely, 6.5 per cent.

The next step in manufacturing requires that this raw cement shall be burned at temperatures of from 1400 to 1600° C. It is then cooled, and a small percentage of gypsum is added. The mixture is then pulverized to such a fineness that at least 92 per cent passes through a No. 100 sieve and 75 per cent through a No. 200 sieve. It is then conveyed to storage for packing and shipment.

Exposure. The dustier occupations involve exposure to dust containing from 1 million to 105 million particles under 10 micra in the longest dimension per cubic foot of air. In the least dusty place the exposure varied from 400,000 to several million dust particles per cubic foot of air. Variations in amount of dust at the same place at different times were wide, depending in great measure on the direction and velocity of the wind and certain other factors.

Chemical analysis showed that lime constituted about 60 per cent of the cement manufactured in the plant under study, and silica about 20 per cent. Iron and aluminum oxids, magnesium oxid, and calcium sulphate were some of the other more important constituents of the cement.

TABLE 1.—CHEMICAL COMPOSITION OF DUST BREATHED BY EMPLOYEES IN SPECIFIED DEPARTMENTS OF A CEMENT PLANT.*

Constituents calculated as follows:	Crusher houses, %.	Stone house, %.	Raw mill, %.	Kiln room, %.	Finishing mill, %.	Bag house, %.	Packing house, %.
Silica (SiO_2)	15.70	17.80	17.00	15.00	18.00	21.30	21.20
Iron and aluminum oxids (R_2O_3)†	6.20	9.10	7.10	4.20	7.30	7.50	8.40
Lime (calcium oxid) (CaO)	41.93	36.11	37.71	38.11	60.18	54.56	60.88
Magnesium oxid (MgO)	2.64	2.46	2.17	2.06	2.61	2.68	2.97
Calcium sulphate (expressed as SO_3)	....	....	.....	....	4.08	2.18	1.75
Loss on ignition (carbon dioxid, water, organic matter)	33.45	34.30	36.02	40.40	7.90	11.70	4.75
Totals	99.92	99.77	100.00	99.77	100.07	99.92	99.95

* The chemical analysis of dust in the coal house was as follows: volatile combustible matter (sulphur, 2.51 per cent), 27.05 per cent; fixed carbon, 46.85 per cent; ash, 26.1 per cent.

† The symbol R stands for both iron and aluminum, since these two oxids were determined as a whole.

Petrographic analysis showed that the proportion of uncombined silica (in the form of quartz) was about 6.5 per cent in all departments before the cement was burned in the kilns. The burning of the raw cement in the kilns produced chemical changes, so that much of the free silica combined with the various chemical elements

in the raw material to form silicates, leaving only about 1 per cent of free silica (quartz) in the finished cement.

The chemical analysis of the finished product has been given above; the petrographic analysis of a sample of cement dust taken from the air of the packing house was found to contain no recognizable grains of calcium carbonate or any claylike material, but appeared to contain about 1 per cent of quartz grains. The dust in the packing house is similar in nature to that found in the departments following the kiln rooms. The finished cement apparently contains, therefore, about 1 per cent of silica in the free state.

From the foregoing statements, it is apparent that the worker in a cement mill is exposed to free crystalline silica, or quartz, in percentages indicated below:

TABLE 2.

		Number of particles per cubic foot.	Free silica, per cent.
Raw cement	Quarry	2,485,000	
	Raw mix room	19,861,000	6.5
	Raw mill	92,035,875	
Finished cement	Kiln room	8 to 20 million	
	Finishing mills	8 to 62 "	1.0
	Bag house	18 to 32 "	
	Packing house	19 to 40 "	

Disabling Sickness. Sickness rates for specific diseases causing disability among the men on the factory payroll of a rubber company in the State of Massachusetts were available for comparison with the experience of the cement workers. (The cement plant where this study was made is located in the middle Atlantic section where the climate is much milder than that of Massachusetts.) The diseases which occurred more frequently in the cement workers than in the rubber workers were in the order of the magnitude of the excess in disability among the former: (1) bronchitis; (2) diseases of the skin; (3) influenza; (4) diseases of the eyes and ears; (5) diseases of the pharynx and tonsils; (6) rheumatism; (7) diseases of the digestive system; (8) diseases of the nasal fossæ. Respiratory diseases other than those named above occurred at a relatively low rate among the cement workers.

Only 3 cases of pneumonia and only 1 disability from tuberculosis appear to have occurred in an exposure of 763 years of life. The age distribution in both these companies was practically the same, and other factors varied but little. The respiratory problem in this cement plant and probably in others showing similar dust concentrations is apparently confined to diseases of the nasal fossæ, acute bronchitis, and diseases of the pharynx and tonsils, with influenza, or grippe.

Seventy per cent of the diseases of the skin were due to furunculosis. Most of these occurred during the summer months and in

workers in the finishing mill and were caused, no doubt, by the clogging of the sebaceous glands with cement dust and by subsequent infection.

TABLE 3.—COMPARATIVE FREQUENCY OF SPECIFIED DISABILITIES AMONG A GROUP OF CEMENT WORKERS AND AMONG MEN ON THE FACTORY PAYROLL OF A RUBBER COMPANY IN MASSACHUSETTS.*

Diseases causing disability.†	Annual number of absences per 1000.		Ratio to rate for rubber workers.‡	No. of absences.	
	Cement workers.	Rubber workers.		Cement workers.	Rubber workers.
Total disability§	725	318	228	553	3857
1. Bronchitis (99)	50	8	625	38	99
2. Diseases of the skin (151–154)	49	9	544	37	109
3. Influenza, or grippe (11)	206	63	327	157	770
4. Diseases of the eyes and ears (85), (86)	16	5	320	12	60
5. Diseases of the pharynx and tonsils (109)	75	25	300	57	301
6. Rheumatism, acute and chronic (51,52)	34	12	283	26	149
7. Diseases of the digestive system (108, 110–127)	114	46	248	87	555
8. Diseases of the nasal fossæ (97)	94	54	174	72	653
9. Other respiratory diseases (31, 98, 100–107)‖	10	12	83	8	143
Ill-defined and unknown diagnoses (205)	9	38	24	7	464
All other diseases and conditions¶	68	46	148	52	554

Years of life under observation: cement workers, 763; rubber workers, 12,147.

* In both groups only those absences were included which lasted two consecutive working days or longer. The record for the cement workers extended from February 6, 1922, to February 1, 1925; for the rubber workers, from January 1, 1922, to December 31, 1924.

† Title numbers in parentheses are taken from the International List of the Causes of Death, third revision, Paris, 1920.

‡ Sickness rates of the rubber workers = 100.

§ Exclusive of accidents and alcoholism.

‖ Includes 3 cases of pneumonia and 1 of pulmonary tuberculosis among the cement workers.

¶ There were only two infectious diseases among the cement workers; 1 case of measles and 1 of typhoid fever.

The greatest incidence of rheumatism occurred in the two outdoor departments of the plant, the yard and the quarry, and among men in the mechanical department. These groups were exposed to sudden changes of atmospheric conditions because of their environment. Obviously rheumatism is not associated with the dust problem.

Conjunctivitis was the most common affection of the eyes. During the physical examination it was found that the ears of many workers were plugged with cerumen and cement dust. This condition resulted in impaired hearing, but produced no actual disabling illness.

The digestive illnesses causing disability were for the most part confined to the summer months. The rates for such illnesses were higher among the men in the finishing and bagging departments than among those in other departments, perhaps because of the fact that workers in the finishing and bagging departments ingest larger amounts of the dust.

Pneumonoconiosis. The extent of generalized fibrosis of the lungs among these workers was not sufficient to warrant a diagnosis of this disease, as such, by general physical examination. The cases diagnosed as having pneumonoconiosis were found by means of the Roentgen ray. The fibrosis shown on the films was of a bilateral distribution and had also many of the other common characteristics of occupational fibrosis. The general nature of the films indicated that the involvement present was less extensive than that found in other cases from occupations which occasioned exposure to a greater percentage of free silica. There were no cases of disability from this cause, and the extent of the condition was not sufficient in any case to cause clinical symptoms. There were no cases of active tuberculosis found among those workers who had evidence (by Roentgen rays) of an occupational fibrosis. The Roentgen ray films of all the cement workers contained evidence of more calcifications than those in the series made on granite cutters. Granite contains very little calcium.

Pulmonary Tuberculosis. Particular attention was given to men who were found to have any chronic respiratory symptoms or signs; they were given closer observation and more detailed chest examinations, and it is believed that no cases of tuberculosis were missed. Suspected and positive cases of pulmonary tuberculosis totaled 21 among the 570 examined, and in only 2 of these 21 cases were there signs of active disease. In a greater portion there were fibrosis and other signs which were indicative of previous infection, though the disease did not at any time reach the stage where there was subjective clinical evidence of pulmonary tuberculosis. In other words, these cases were of the "closed" type. Regarding the 2 active cases which were found, it was evident from the histories and physical conditions that in these cases the disease had developed before service in the cement industry. One of them was of the chronic fibroid type, and the man knew that he had tuberculosis for many years. He died (near the age of 50 years) about a year after the study had closed. In the other case the man who was younger continued working, and the disease appeared to become quiescent.

The workers of the group which had positive signs of arrested tuberculosis were able to work in the dusty atmosphere without any apparent harm to their old tuberculous lesions. The dusts produced in manufacturing Portland cement in the plant under observation contained free silica in proportion varying from 1 to 6.5 per cent, according to the stage of the manufacturing process, and from

30 to 60 per cent of calcium oxid (lime). The amount of calcium in relation to silica or other constituents of inhaled dust appears to be of importance in the incidence and development of industrial tuberculosis. Two facts in this connection stand out prominently in the study: first, no new cases of tuberculosis were found to have appeared as the result of exposure to cement dust; and second, the cases which had unmistakable evidence of arrested tuberculosis exhibited no tendency to reactivation of the disease. We are led to believe that exposure to dust generated in the manufacture of Portland cement is not provocative of tuberculosis, nor is it a factor in reactivation of arrested disease. The following table is a summarization of the incidence of early pneumonoconiosis and of this condition when complicated by tuberculosis. The tuberculosis was not active.

TABLE 4.—CEMENT WORKERS. RELATION OF YEARS OF EXPOSURE TO ROENTGENOGRAPHIC DIAGNOSIS.

	Years in cement.						
	Up to 5.	5 to 9.	10 to 14.	15 to 19.	20 to 24.	Total.	Percentage.
Negative	3	1	1	1	..	6	11.3
More fibrosis than usual	14	7	1	..	..	22	41.5
More fibrosis than usual, with infection (tuberculosis)	7	1	1	1	..	10	18.9
Early pneumonoconiosis	4	4	3	..	..	11	20.8
Early pneumonoconiosis, with infection (tuberculosis)	1	1	..	2	..	4	7.5
Total	29	14	6	4	..	53	

We have shown[2] that workers can tolerate an exposure to a dust containing 35 per cent of quartz in a concentration of 10 to 20 million particles per cubic foot without having a tuberculosis rate greatly above that of the general population in the registration area of the United States. It is not reasonably to be supposed that cement workers would develop silicosis to any great extent, since the highest silica content in cement dust is only 6.5 per cent. Since they do not have marked silicosis, it is not surprising that they do not show excessive rates of tuberculosis. In the light of these facts we are still unable to state whether or not calcium possesses antisilicotic properties. It is common knowledge that the presence of a latent or concurrent tuberculous infection will cause silicosis to develop more rapidly, and it is quite possible that certain mixtures of dusts may be capable of such effects or the opposite; but more information, both experimental and clinical, is needed to substantiate this theory. It would be a great aid in the amelioration of dust hazards if it were possible to render a harmful dust inert by mixing with it one which has been proved to possess antisilicotic

properties. Such an expedient would obviate the necessity for great expenditures in the installation and operation of ventilating equipment and would do away with the present-day use and abuse of masks.

Summary. In 1928 the cement industry employed about 42,000 men in about 150 manufacturing plants, representing an investment of more than $500,000,000. The greatest concentration of dust was found at a mill where the average number of dust particles under 10 micra was 92 million particles per cubic foot of air. Other dusty locations showed counts which ranged from 22 million to 63 million particles per cubic foot of air. Variations in the dust count were found to depend to a great extent upon the direction and velocity of the wind and other atmospheric conditions.

Chemical analysis showed that lime constituted about 62 per cent of cement, and silica about 22 per cent. Alumina, iron oxid, magnesia, and sulphur trioxid are the other more important constituents of cement. Petrographic analysis showed that the proportion of free silica (quartz) varied from 6½ per cent in the crusher houses, raw mill, and stone house to about 1 per cent in the finished cement.

The frequency of disability on account of respiratory diseases among the cement workers was twice as great as the average respiratory rate among employees of eleven manufacturing plants in relatively nondusty industries. The highest rate for all respiratory diseases in any of these establishments was 30 per cent below the rate of the cement workers.

Diseases of the skin gave a high rate of disability, and furunculosis (boils) was the cause of 70 per cent of the absences which were due to skin diseases.

The highest incidence of rheumatism occurred in the outdoor workers and there was a seasonal variation of the disease.

Conjunctivitis was the most frequent disability of the eyes.

The men employed in the finishing, bagging and packing departments had a rate almost twice as high as for those in the other departments for gastrointestinal disturbances. There was a marked seasonal variation for this condition.

There was a seasonal variation in respiratory diseases, which would be expected; the peak was reached in February. The respiratory rate varied more in accordance with general physical condition than with age.

Of the 570 workers examined, 21 (3.7 per cent) were diagnosed as having either positive or suspected pulmonary tuberculosis. In only 2 cases, however, was the disease active at the time of the first series of special chest examinations, and neither appeared to progress as a result of exposure to dusts. The history of both cases indicated that the disease had developed before their work in the cement industry. One of them gave a history of infection last-

ing many years, of chronic fibroid type, and he died suddenly about a year after cessation of the period of observation. The other became a quiescent case while working and during the progress of our study.

The other cases, excepting the suspects on whom we were unable to make a positive diagnosis of tuberculosis, seemed to have developed and healed their tuberculous lesions prior to exposure to cement dust, and there was no evidence that their lesions were reactivated during the period of their dust exposure.

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THE EFFECT OF IRRADIATED ERGOSTEROL ON CALCIFICATION OF TUBERCLES IN EXPERIMENTAL TUBERCULOSIS.

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The value of vitamin D in stimulating calcification has been demonstrated in rickets and osteomalacia. The fact that calcification of tubercles plays an important part in the healing of tuberculosis has led to considerable investigation concerning the effect of irradiated ergosterol on tuberculous lesions.

Levaditi and Li[1] injected human tubercle bacilli into the testicles of rabbits and found that the oral administration of so-called "subtoxic" doses (5 mg. per kilo) of irradiated ergosterol caused intense calcification of tubercles which had developed in the lungs and testicles. Calcium deposits were not found in the normal tissues. Spies[2] administered massive doses of irradiated ergosterol (viosterol) to rabbits in which both acute and chronic bovine tuberculosis had been produced by intravenous injection of a heavy suspension of avirulent tubercle bacilli. He noted marked calcification of the caseous tubercles in the lungs, liver and spleen. Later Walker and Spies[3] obtained similar results in guinea pigs with acute bovine tuberculosis by feeding irradiated ergosterol. Policard, Ravault and Barral[4] were able to produce calcium deposition in the caseated tubercles of guinea pigs with bovine tuberculosis, but they also noted deposition of calcium in normal organs. Simonnet and

Tanret[5] showed, by chemical analysis, that irradiated ergosterol, when administered to normal and tuberculous rabbits, caused a rapid increase in the amount of calcareous salts in the lung tissue. This increase was approximately four times as great in the tuberculous rabbits as in the healthy animals. Loewy and Gruninger[6] injected a culture of human tubercle bacilli subcutaneously into the abdominal wall of guinea pigs and studied the effect of administering irradiated ergosterol (vigantol) alone and in combination with calcium gluconate. Their results indicated that the animals had a diminished resistance to the disease when the vigantol and calcium gluconate injections were combined.

There are several factors which prevent a satisfactory evaluation of the foregoing reports. In the first place, much of the work was conducted on rabbits and it is well known that these animals show an anomalous susceptibility to the calcifying effect of both irradiated ergosterol and calcium salts. Preparations of irradiated ergosterol other than viosterol were employed in some instances and a number of the preparations were not biologically standardized. In addition, the various types and strains of tubercle bacilli may influence the lesions so that comparison of results is difficult. Recently, Spies[7] was unable to produce calcification of tuberculous lesions in guinea pigs with experimental avian tuberculosis, using massive doses of viosterol.

Experimental. Two series of experiments (Series A and B) were conducted, employing for each series 13 guinea pigs, weighing about 325 gm. each. Series A (see table) was divided into Groups I, II, III and IV, and Series B into Groups V, VI, VII and VIII. One one-hundredth milligram of a known virulent culture of human tubercle bacilli (Strain H119)* was injected intramuscularly into the right groins of 10 of the 13 animals in Series A (Groups I, II and III). The remaining 3 guinea pigs in this series were not inoculated with tubercle bacilli and served as controls for the viosterol dosage (Group IV). In Series B an attempt was made to simulate tuberculosis as it occurs in human beings by producing secondary tuberculous lesions. Accordingly, a preliminary sensitizing injection of a known avirulent strain of human tubercle bacilli (0.1 mg. of Strain R1)† was given intramuscularly to each animal in the second series (Nos. 14 to 26) and, 6 weeks later, the virulent tubercle bacilli (H119) were injected into these animals. The experiment, as described for Series A, was duplicated in detail with Series B (see table) commencing 6 weeks after the animals received their preliminary sensitizing injections.

All animals were fed a normal laboratory diet to which 0.75 per cent of calcium carbonate was added. In addition to this food

* Furnished through the courtesy of Dr. Robert Bloch of the University of Chicago.
† Ibid.

TABLE 1.—RÉSUMÉ OF INVESTIGATION.

Group No.	Viosterol, 1000X (daily dosage).	Animal No.	Lymph nodes.		Spleen.		Liver.		Lungs.		Heart.		Aorta.		Kidneys.		Blood serum (mg. per 100 cc.).	
			Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Ca.	P.
							SERIES A.											
							Injected intramuscularly with $\frac{1}{100}$ mg. of virulent strain (H119) of human tubercle bacilli.											
I	0.1 cc., 1st to 14th day	1	C.	+++++	Tub. and C.	+++	Tub. and C.	○	Tub.	○	Nor.	○	Nor.	○	No tub. or C.	○	12.9	8.2
	0.2 cc., 15th to 84th day	2	"	+++++	" "	+++	" "	○	"	○	"	○	"	○	" "	○	12.2	7.5
		3	"	+++++	" "	+++	" "	+++	"	+++	"	○	"	○	" "	○	11.7	7.4
		4	"	+++++	" "	+++++	" "	○	"	○	"	○	"	○	" "	++	..	..
II	No viosterol, 1st to 14th day	5	"	+++++	" "	+++++	" "	+++	"	○	"	○	"	○	" "	+++++	13.6	8.0
	0.2 cc., 15th to 30th day	6	"	+++++	" "	+++++	" "	○	"	○	"	○	"	○	" "	+++++	13.0	9.6
	1.0 cc., 31st to 84th day	7	"	+++++	" "	+++	" "	○	"	○	"	○	"	○	" "	+++	..	..
	(No. 8 died on 30th day)	8	"	+++	" "	++	" "	○	Occ. tub.	○	"	○	"	○	" "	○	..	..
III	(Tuberculous controls)	9	"	○	" "	○	" "	○	Tub.	○	"	○	"	○	" "	○	11.3	5.3
	No viosterol	10	"	○	" "	○	" "	○	"	○	"	○	"	○	" "	○	11.6	5.1
IV	(Nontuberculous controls)											○						
	0.1 cc., 1st to 14th day	11	Nor.	○	Nor.	○	Nor.	○	Nor.	○	"	○	"	○	" "	++	11.7	..
	0.2 cc., 15th to 84th day	12	"	○	"	○	"	○	Beg. pneum.	○	"	○	"	○	" "	○	..	..
	(No. 12 died on 44th day)	13	"	○	Sl. foll. hyper.	○	Sl. fat. degen.	○	Pneum.	○	"		"	○	Sl. cl. swell.	○	..	..
	(No. 13 died on 61st day)																	
							SERIES B.											
							Preliminary sensitization with avirulent strain of human tubercle bacilli (R1)—$\frac{1}{10}$ mg. intramuscularly. After 6 weeks virulent strain (H119) injected as in Series A.											
V	No viosterol, 1st to 44th day	14	Much C.	○	Tub.; confl. C.	○	Tub.; confl. C.	○	Many tub.	+	Nor.	○	Nor.	○	No tub. or C.	○	11.3	5.5
	0.1 cc., 45th to 60th day	15	"	○	" "	○	" "	○	" "	+	"	○	"	○	" "	○	11.8	6.9
	0.2 cc., 61st to 84th day	16	"	○	" "	○	" "	○	" "	+	"	○	"	○	" "	○	..	..
		17	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	11.6	7.1
VI	No viosterol, 1st to 60th day	18	"	○	" "	○	" "	○	" "	○	"	○	"	○	C., rt. kidn.	○	..	..
	0.2 cc., 61st to 76th day	19	"	○	" "	○	" "	○	" "	○	"	○	"	○	No tub. or C.	○	9.4	6.9
	1.0 cc., 77th to 83d day	20	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	..	..
		21	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	..	..
VII	(Tuberculous sensitized controls)	22	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	10.4	3.7
	No viosterol	23	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	..	..
		24	"	○	" "	○	" "	○	" "	○	"	○	"	○	" "	○	..	..
VIII	(Nontuberculous sensitized controls)																	
	No viosterol, 1st to 44th day	25	Nor.	○	Nor.	○	Nor.	○	Nor.	○	"	○	"	○	" "	○	12.0	7.7
	0.1 cc., 45th to 60th day	26	"	○	"	○	"	○	"	○	"	○	"	○	" "	○	11.8	8.0
	0.2 cc., 61st to 84th day																	

+++++ = extensive; ++++ = marked; +++ = moderate; ++ = slight; + = traces; ○ = no calcification; C. = caseation; Tub. = tubercles.

mixture daily rations of carrots were given. The high calcium content in the food mixture was supplied in order to prevent bone demineralization. To check the calcium content of the bones, roentgenograms of all of the animals were taken at the beginning of the investigation and repeated at monthly intervals. The final Roentgen rays showed exactly the same bone density as the initial plates. Each of the 8 groups of animals was kept in a separate cage. The irradiated ergosterol used in this investigation was a special preparation (viosterol in oil 1000X)* possessing ten times the potency of viosterol in oil 250 D, and was administered by mouth with calibrated pipettes.

Each guinea pig in Group I (Nos. 1, 2, 3 and 4) was given daily 0.1 cc. of this preparation of irradiated ergosterol from the 1st to the 14th day, and 0.2 cc. from the 15th day until the completion of the experiment (85th day). Our aim in starting the administration of viosterol to this group before the development of tuberculous lesions was to note any possible prophylactic value.

The animals in Group II (Nos. 5, 6, 7 and 8) were given 0.2 cc. of viosterol daily from the 15th to the 30th day. On the 30th day animal No. 8 died during a period of extremely hot weather. The viscera of this animal, on postmortem examination, did not show any gross calcification of the tuberculous lesions. (Microscopic findings will be discussed later). Therefore, the viosterol dosage for the remaining 3 animals (Nos. 5, 6 and 7) in this group was increased to 1 cc. daily, which was continued from the 31st day until the end of the experiment. During this period the viosterol was omitted every 4th or 5th day.

Group III consisted of 2 tuberculous control animals (Nos. 9 and 10) which did not receive viosterol. Group IV included the 3 nontuberculous control animals (Nos. 11, 12 and 13). This group was given 0.1 cc. of viosterol daily for 14 days and 0.2 cc. of viosterol from the 15th day until the end of the experiment, the dosage being the same as in Group I. Two of these animals died of pneumonia, No. 12 at 6 weeks and No. 13 at 8 weeks.

In Series A the animals showed a steady gain in weight for 10 weeks, followed by a period of stationary weight or slight loss. The average total gain for each animal was 150 gm. The tuberculous animals in this series (Nos. 1 to 8) which received viosterol lost only 25 to 35 gm. during the last 2 weeks of the experiment. The animals in Series B gained steadily for 9 weeks, the average total gain being 200 gm. After the 9th week the animals in Groups V, VI and VII began to lose weight perceptibly. The 2 sensitized guinea pigs (Nos. 25 and 26) which were not inoculated with the virulent culture but were given viosterol, continued to gain weight until the end of the experiment. The experiment was ended on the

* Supplied through the courtesy of Mead Johnson & Co.

85th day when several animals in Series B began to lose weight rapidly.

In terminating the experiment each animal was given a lethal ether anesthetic and sufficient heart's blood was withdrawn during the anesthesia for serum calcium and phosphorus determinations.* Compared with an average blood calcium level of 11.6 mg. per cc. and an average phosphorus of 5.4 mg. obtained by making determinations on the blood of 30 normal guinea pigs, all animals in Groups I and II showed both hypercalcemia and hyperphosphatemia. The calcium values were from 1 to 2 mg., and phosphorus from 2 to 4 mg. above the average normal levels. No significant variations from the normal were found in the remaining animals except those in Group VIII (Nos. 25 and 26), the nontuberculous sensitized controls which were given viosterol. In this group the average calcium level was 11.9 mg. and the phosphorus 7.8 mg.

Necropsies were performed immediately after the death of the animals. Tissues for examination were taken from the lymph nodes (inguinal, iliac and tracheobronchial), spleen, liver, lungs, heart and aorta. They were fixed in 10 per cent formalin and imbedded in paraffin. In order to identify the calcium deposition, all sections were stained in duplicate, one set with hematoxylin and eosin and the other by the silver method of von Kossa. Calcium deposits could be identified by the hematoxylin and eosin stain as readily and clearly as with the von Kossa method.

On gross examination the animals in both series showed typical lesions of miliary and caseous tuberculosis involving the lymph nodes, spleen, liver and lungs. One kidney of animal No. 14 (Group V, Series B) presented a few small areas of caseation. Tuberculous renal lesions could not be found in any of the other animals. The lymph nodes were enlarged and showed extensive caseation in all animals except the nontuberculous controls. The heart and aorta of all of the animals appeared normal. Although typical tuberculous lesions were produced in both Series A and B, the sensitized group showed a more intense tuberculous involvement. The spleen and liver of the animals in Series B were markedly enlarged and contained large confluent areas of caseation. The cut surfaces of the spleen and liver of the inoculated animals in Series A which had received viosterol presented several hard, white, calcareous spicules, 1 to 2 mm. in diameter. Microscopic examination confirmed the gross findings.

In Series A a striking illustration of the calcifying effect of viosterol on tuberculous tissues was found. The tuberculous animals which did not receive viosterol (Group III) presented lesions with the same degree of tissue involvement as those to which viosterol

* Determinations were made in the Department of Chemistry. (Calcium by Clark-Collip modification of the Kramer-Tisdall method, and phosphorus by the Briggs modification of the Bell-Doisy method.)

was administered. Calcification was absent in this group (III). In Group I (Animals 1, 2, 3 and 4) calcification occurred in the lymph nodes and spleen of each animal. In addition, Animal 3 showed calcification of the central necrotic area of a few tubercles in the lungs (Fig. 1) and liver. One tubercle in the liver was completely calcified and particles of calcium could be detected in the necrotic areas of the other tubercles. Animal 4 showed a few small deposits of calcium in the walls of the bloodvessels and tubules of the kidney without any tuberculous lesions.

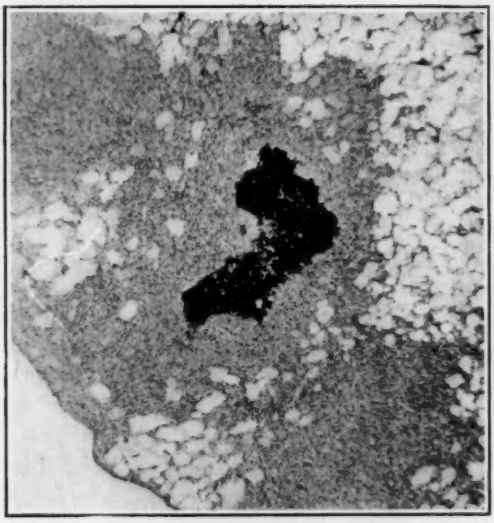

FIG. 1.—Section of lung. Hematoxylin and eosin stain. Magnification ×20. Center of one tubercle shows marked calcium deposit (black area).

In Group II (Animals 5, 6 and 7), extensive calcium placques were found in the lymph nodes. In some of the lymph nodes calcification occurred almost entirely at the periphery of the caseous areas, but a few calcium deposits were also noted in the centers of the necrotic areas. The spleen (Fig. 2) in each animal of this group showed marked calcification. Many tubercles were completely calcified, one being entirely surrounded by fibroblastic tissue. Moderate calcification occurred in the liver of Animal 5. There was an absence of calcification in the lungs of this group (II). Calcification of the walls of the renal bloodvessels and extensive deposits of calcium in the tubules of the kidneys occurred in each animal of this group. Spies and Glover[8] reported similar renal lesions in normal rabbits with the administration of repeated massive doses of viosterol (3 to 10 cc. viosterol 1000X) at intervals of 1 to 4 days for a period of 60 days.

It was interesting to note a very slight calcification of the wall

of the renal arterioles in Animal 11, a nontuberculous guinea pig which received viosterol for the entire period of investigation. All other tissues of this animal were normal. The other 2 nontuberculous control animals (Nos. 12 and 13) of this group (IV) which died earlier in the experiment showed no calcification in the kidneys. These 2 animals had received viosterol for, respectively, 1½ and 2 months at the time of their death. It would appear from these facts that the daily administration to guinea pigs of 0.2 cc. viosterol 1000X may be continued safely for at least 2 months, but less than 84 days. This daily dosage is equivalent to 6 cc. per kilo of viosterol 250 D.

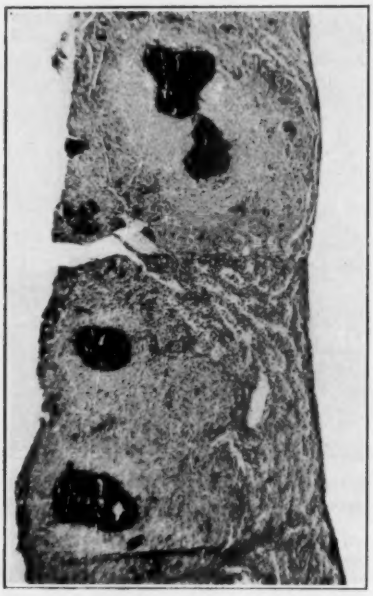

FIG. 2.—Section of spleen. Hematoxylin and eosin stain. Magnification ×20. Marked calcification (black areas) of several tubercles.

In Series B, Group VIII (Nos. 25 and 26), the sensitized animals which did not receive a subsequent injection of virulent bacilli, presented normal tissues and no calcification. The microscopic sections of Series B, aside from this group, showed many typical tubercles and areas of caseation in the spleen and lungs of all the animals. The lymph nodes and liver presented extensive caseous areas. In the necrotic portions of the tubercles in the lungs of 3 animals in Group V, there were a few minute calcium-staining particles but no definite calcification. Calcification was absent in all other sections of Series B.

Summary. 1. In two series of experiments 10 guinea pigs were injected intramuscularly with a virulent culture of human tubercle bacilli, 3 serving as nontuberculous controls. In Series B an attempt

was made to simulate tuberculosis as it occurs in human beings. The procedure was the same as in Series A, except that a preliminary injection of a known avirulent strain of human tubercle bacilli was given to all 13 animals 6 weeks before the virulent culture was introduced. The effect of viosterol (administered orally) upon the lesions produced was investigated.

2. This demonstrated in a striking manner that the daily administration of viosterol in oil 1000X, in doses varying from 0.1 to 1 cc., causes deposition of calcium in the caseous tubercles in guinea pigs. The blood of the animals so affected showed both hypercalcemia and hyperphosphatemia. There was no evidence of calcium depletion in the roentgenograms of the bones.

3. Spontaneous calcification did not occur in the tuberculous animals which received no viosterol.

4. The most intense calcification was found in the lymph nodes and spleen of those tuberculous animals which were given the largest doses of viosterol. Calcium deposits were noted only in the caseated areas.

5. Undesirable calcification results if viosterol is given over a prolonged period in excessively large doses. In our investigation 0.2 cc. of viosterol in oil 1000X was administered daily for 2 months without any apparent harm. When continued for 84 days undesirable calcification occurred. This dosage is equivalent to 6 cc. per kilo of viosterol in oil 250D.

6. Calcification was present in the walls of the renal bloodvessels and in the renal tubules of both the tuberculous and nontuberculous animals which received daily amounts of viosterol in oil 1000X varying from 0.5 cc. to 1 cc. for more than 2 months. No calcium deposits were seen in the apparently normal portions of any of the other organs.

7. The tuberculous animals which received the preliminary sensitizing injection did not show any definite calcification, possibly because the effect of viosterol is diminished in the presence of a fulminating secondary tuberculous process.

8. The calcification of tubercles which was noted in this investigation is, in our opinion, not merely an expression of simple tissue necrosis but rather a reparative process. If it is permissible to calculate a human dosage of viosterol on a basis of weight, the maximum daily dosage given to our guinea pigs corresponds to a dosage of 300 cc. of viosterol in oil 250D, if given to a child weighing 22 pounds. We refrain from making any recommendation concerning the clinical application of viosterol in tuberculosis because of possible renal damage. Future research may determine an optimum dosage which may have clinical value in certain types or stages of the disease.

NOTE.—We are greatly indebted to Dr. Robert Bloch of the University of Chicago and Drs. Otto Saphir and David Cohen of the Michael Reese Hospital for their assistance and advice.

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THE EVOLUTION OF TUBERCULOSIS IN THE HUMAN LUNG.

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As revealed by Roentgen ray examinations, primary or initial infections by the Mycobacterium tuberculosis present a varied array of intrathoracic lesions for which the general term Tuberculosis of the Childhood Type was adopted by the American Sanatorium Association[1] in 1929. In the past various designations such as hilum tuberculosis, masked juvenile tuberculosis, infantile tuberculosis, pretuberculosis, latent tuberculosis, concealed tuberculosis, paratuberculosis, epituberculosis, splenopneumonia, gelatinous pneumonia, collateral inflammatory edema, glandular calcifications, Ranke's primary complex, Ghon tubercles, and others have been used in connection with descriptions of primary tuberculosis. The simplification of terminology, accomplished by the American Sanatorium Association, probably will tend to focus attention on primary tuberculosis as a clinical entity manifested by a variety of lesions which collectively represent different retrogressive developmental stages of primary tuberculosis as it customarily occurs in the human lung, whereby the initial or early parenchymal and perihilum infiltrations present in the lung, whether large or small, later slowly resolve to be replaced eventually either by calcified hilum glands alone, or by Ghon tubercles associated with calcium deposits in the adjacent lymph nodes. The end stage of the lesion produced by a primary implantation of tubercle bacilli in the lung parenchymal and the subsequent spread of the infection to the regionally related lymph nodes (which commonly occurs, Refs. 2 to 23 incl.) often is represented by permanent scars known as Ghon tubercles associated with calcified hilum glands, which collectively constitute Ranke's primary complex. In the earliest stage of this pathologic process, relatively benign parenchymal infiltrations of varied sizes form the most striking feature revealed by Roentgen ray examination. Cases representative of this early stage of (massive?) primary pulmonary tuberculosis have been

reported by various authors (see Refs. 24 to 48 incl.). Often in the reported cases which had this type of lesion the disease was relatively benign, and a general tendency was noted for extensive parenchymal lesions to resolve slowly. Many of these children were followed over long periods of time, giving the authors an opportunity to observe complete restoration to normal health occurring frequently in young infants as well as in older children.

Additional data bearing on this subject of primary tuberculosis are presented in the following report based on observations on 1687 children examined at Lymanhurst School for Tuberculous Children in Minneapolis. Each individual included in this group received an intracutaneous injection of 0.1 mg. of old tuberculin, and during periods of observation ranging from 4 to 11 years, the positive tuberculin reactors have had repeated Roentgen ray and physical examinations. The system established at Lymanhurst by Dr. F. E. Harrington, Commissioner of Health, whereby follow-up contacts are made between the patients and the Minneapolis Public Health Nurses, has offered an opportunity to observe the clinical course of primary tuberculosis in the same individual over a period of a few to several years. This follow-up study of a fairly large group of infected children, in which epidemiologic investigations also have been made, has revealed a clinical picture of primary tuberculosis in children, which during the past 11 years has revolutionized many of the opinions formerly entertained by the members of Lymanhurst Medical staff, not only with regard to the ability of an infant or child to survive a severe primary tuberculous infection of the lungs, but also concerning the customary changes which occur in these lesions as the years go by, as well as concerning the relationship of primary tuberculosis to the adult type of the disease.

The data for the 1687 children (sexes combined) included in the survey are recorded in Table 1, in which the 1108 cases who had a negative reaction to 0.1 mg. of tuberculin are separated from the 579 individuals who had a positive reaction to this amount of old tuberculin. Of the 1108 Mantoux-negative cases, repeated Roentgen ray films of the chest were found to be consistently negative in an average of 90.1 per cent (998 cases) of this group. In general, however, during the span of life included in this study (0 to 17 years) the percentage of negative Roentgen ray examinations tended to decline as age increased. In certain instances lesions were found in the Mantoux-negative group (intrathoracic, glandular calcifications and Ghon tubercles [51 cases, Table 1] which were indistinguishable from those characteristic of certain [late] stages of primary tuberculosis [childhood type of tuberculosis]). This group of 51 cases constituted 4.6 per cent of the 1108 children who had a negative reaction to 0.1 mg. of old tuberculin. Each of these children was given a second Mantoux test, using 1 mg. of old tuberculin, to which not a single individual reacted. This observa-

TABLE 1.—TYPES OF INTRATHORACIC LESIONS FOUND BY ROENTGEN EXAMINATION FOR EACH AGE GROUP IN CHILDREN WITH NEGATIVE AND POSITIVE MANTOUX TESTS.

Age, yrs.	No. of cases.	Negative on Roentgen ray exam., per cent.	Lesions characteristic of primary tuberculosis (childhood type).						Adult type of tuberculosis, per cent.	Pleural thickening, per cent.	Bronchiectasis, per cent.	Pneumonia, per cent.	Pneumothorax, per cent.
			Resolving parenchymal, per cent.	Questionable calcification, per cent.	Slight calcification, per cent.	Moderate calcification, per cent.	Marked calcification, per cent.	Ghon tubercles, per cent.					
Cases Reacting Negative to the Intracutaneous Injection of 0.1 Mg. of Old Tuberculin. Uninfected Group.													
0 to 1	27	96.3 (26)*	...	...	...	...	...	...	...	...	3.7 (1)		
2 to 3	57	98.2 (56)	...	...	...	...	...	...	...	1.8 (1)			
4 to 5	112	94.6 (106)	...	...	1.8 (2)	...	...	...	...	2.7 (3)	...	0.9 (1)	
6 to 7	161	93.8 (151)	...	1.2 (2)	1.2 (2)	...	...	...	...	2.5 (4)	1.2 (2)		
8 to 9	176	90.9 (160)	...	1.1 (2)	4.0 (7)	...	...	0.6 (1)	...	2.8 (5)	0.6 (1)		
10 to 11	199	90.5 (180)	...	2.0 (4)	3.0 (6)	...	...	...	...	3.0 (6)	1.0 (2)	0.5 (1)	
12 to 13	176	83.5 (147)	...	2.3 (4)	2.8 (5)	1.2 (2)	...	...	...	8.5 (14)	1.1 (2)	1.1 (2)	
14 to 15	144	89.6 (129)	...	0.7 (1)	2.8 (4)	...	0.7 (1)	...	...	3.5 (5)	2.1 (3)	0.7 (1)	
16 to 17	56	76.8 (43)	...	3.6 (2)	8.9 (5)	...	...	1.8 (1)	...	7.1 (4)	...	1.8 (1)	
Totals and av.	1108	90.1 (998)	...	1.4 (15)	2.8 (31)	0.2 (2)	0.1 (1)	0.2 (2)	...	3.8 (42)	1.0 (11)	0.5 (6)	
Cases Reacting Positive to the Intracutaneous Injection of 0.1 Mg. of Old Tuberculin. Infected Group.													
0 to 1	9	77.8 (7)	11.1 (1)	11.1 (1)									
2 to 3	13	53.1 (7)	30.8 (4)	...	7.7 (1)	7.7 (1)							
4 to 5	39	59.0 (23)	15.4 (6)	...	15.4 (6)	2.6 (1)	...	5.1 (2)	...	2.6 (1)			
6 to 7	55	45.5 (25)	7.3 (4)	10.9 (6)	20.0 (11)	3.6 (2)	1.8 (1)	9.1 (5)	...	1.8 (1)			
8 to 9	90	43.3 (39)	6.7 (6)	15.6 (14)	11.1 (10)	4.4 (4)	4.4 (4)	12.2 (11)	...	2.2 (2)			
10 to 11	91	47.3 (43)	2.2 (2)	7.7 (7)	11.0 (10)	7.7 (7)	...	18.7 (17)	...	5.5 (5)			
12 to 13	92	40.2 (37)	...	10.9 (10)	13.0 (12)	5.4 (5)	1.1 (1)	14.1 (13)	3.3 (3)	12.0 (11)			
14 to 15	115	43.5 (50)	2.6 (3)	5.2 (6)	15.7 (18)	4.3 (5)	2.6 (3)	11.3 (13)	4.3 (5)	7.8 (9)	1.7 (2)	...	0.9 (1)
16 to 17	75	34.7 (26)	1.3 (1)	8.0 (6)	16.0 (12)	6.7 (5)	5.3 (4)	8.0 (6)	6.7 (5)	12.0 (9)	1.3 (1)		
Totals and av.	579	44.4 (257)	4.7 (27)	8.6 (50)	13.8 (80)	5.2 (30)	2.2 (13)	11.6 (67)	2.2 (13)	6.6 (38)	0.5 (3)	...	0.2 (1)

* Actual number of cases in parenthesis.

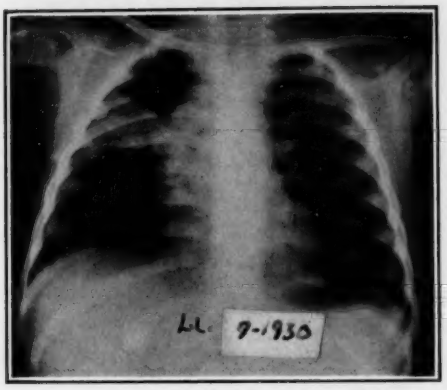

FIG. 1.—Roentgen ray plate, showing parenchymal infiltration (right) due to a primary tuberculous infection of a child, aged 13 months. Plate taken, July, 1930.

FIG. 2.—Roentgen ray taken, April, 1932, of the same child, showing parenchymal infiltration almost completely resolved and replaced by a cluster of calcium deposits. Resolution and complete development of Ghon tubercle required over 21 months in this case during which time this child has not experienced a single day of illness.

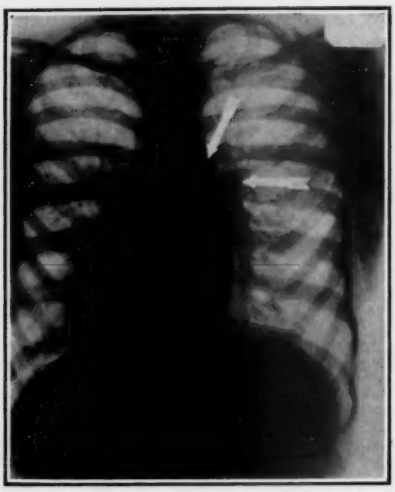

FIG. 3.—Roentgen ray taken, in 1921, of boy, aged 10 years, showing2 conspicuous calcified hilum glands on the right identifying the location of his primary tuberculous lesion.

FIG. 4.—Roentgen ray taken, 1932, of same case as Fig. 3. Shows large calcified gland on the right with no evidence of renewed activity in its vicinity. The other calcified gland is not visualized on this plate. We now find an extensive adult type of tuberculosis throughout the left lung with a small similar type of lesion in the periphery of the right lung. This boy died shortly after this film was taken.

tion strongly suggests that the 51 children in this retested group never had been infected by the tubercle bacillus, in spite of the Roentgen ray evidence to the contrary. The conclusion seems justified, therefore, that in children who have never experienced a primary infection by the Mycobacterium tuberculosis as indicated by their negative reaction to relatively large doses of old tuberculin, lesions caused by nontuberculous infections are occasionally found which on the chest films are indistinguishable from those characteristic of primary tuberculosis. This applies particularly to questionable and slight degrees of intrathoracic glandular calcifications (46 cases, Table 1) in which instances the apparent discrepancies may be due in a measure to unavoidable error on the part of an experienced roentgenologist in identifying small calcium deposits. At times the roentgenologist is correct in interpreting the presence of intrathoracic calcium deposits in Mantoux-negative children, since certain nontuberculous infections produce lesions that calcify (Kudlich)[49] and occasionally these scars may be fairly large, conspicuous and easily identified. Some of the cases of this type may be examples of aspergillus infection. Their incidence in tuberculin-negative children is rather low, however, for among the 1108 Mantoux-negative reactors moderate and marked degrees of glandular calcification and Ghon tubercles associated with calcified glands occurred in a combined total of only 5 cases (Table 1) or 0.45 per cent of this group of children. The data indicate, therefore, that Roentgen ray findings which might be construed as constituting strong evidence of the presence of primary tuberculosis are rarely discovered in children who have a definitely negative Mantoux test.

In a few instances noncalcified lesions due to conditions other than tuberculosis were found in the group of negative tuberculin reactors. These lesions included pleural thickenings (42 children), bronchiectasis (11 children) and pneumonia (6 children), and combined they constituted about 5.3 per cent of this entire group of 1108 children. If the cases found to have questionable and slight intrathoracic glandular calcifications are excluded on the basis of erroneous interpretation of their chest films, under these circumstances lesions due to nontuberculous conditions occurred over eleven times as frequently among the 1108 Mantoux-negative cases, as did conspicuous, easily recognized lesions which are definitely characteristic of primary tuberculosis (moderate and marked calcifications and Ghon tubercles). On the whole, then, the data indicate that in children under 18 years of age who never have been infected by the tubercle bacillus the chest films are negative in the great majority of cases, and then when intrathoracic pathology is revealed by Roentgen ray examination, these findings usually are typical of lesions produced commonly by various nontuberculous infections.

Among the infected children (positive Mantoux reactors) entirely

different conditions were found. Of this group of 579 individuals less than half (44.4 per cent, Table 1) were reported as entirely normal on Roentgen ray examination as compared with an average of 90.1 per cent of similarly negative cases for the group of 1108 children who did not react to tuberculin. The incidence of intrathoracic lesions demonstrable by Roentgen ray films found in the 579 infected children (55.6 per cent) greatly exceeded that (9.9 per cent) discovered in the uninfected cases, and this increase in pathologic findings noted for the former, as compared with the latter group of children, resulted largely from scars produced by the primary tuberculous infections which the positive Mantoux reactors had experienced. The influence of primary tuberculosis in greatly increasing the incidence of lesions demonstrable by chest films becomes evident on further analysis of the data, according to which lesions typical of the primary or childhood type of tuberculosis (resolving parenchymal infiltrations, calcified intrathoracic glands and Ghon tubercles) were found in a total of 46.1 per cent (279 cases, Table 1) of the 579 infected children, as compared with an incidence of 4.6 per cent (51 cases) for similar lesions in the Mantoux-negative group. Attention is also called to the fact that in the infected group the percentage of lesions typical of the childhood type of tuberculosis (46.1 per cent), greatly exceeded the relative incidence (5.3 per cent) of lesions reported for the noninfected group resulting from all nontuberculous pulmonary infections combined. In the positive Mantoux series this is also true when the cases who had questionable and slight calcifications of the hilum glands are excluded. Thus an additional statement seems justified, to the effect that primary pulmonary infections by the Mycobacterium tuberculosis occurring during childhood produce conspicuous intrathoracic lesions which are practically unmistakable on the chest film, the incidence of which greatly exceeds that of lesions resulting from all other pulmonary infections combined.

The prevalence of lesion due to various nontuberculous conditions (pleural thickenings, bronchiectasis, pneumonia and pneumothorax) found in the group of tuberculin-positive children, in general, did not differ greatly from that observed for those who had a negative Mantoux reaction. The only essential difference noted between the two groups with respect to these conditions was the greater relative frequency of pleural thickening in the cases who had a positive tuberculin reaction. The increase noted for this type of lesion no doubt was due in part, if not entirely, to the tuberculous infections which this group had experienced as indicated by the observation that primary tuberculous infections frequently produce thickenings of the pleura.

The primary or childhood type of tuberculosis discovered in these children was exemplified by various lesions which may be classed conveniently into three main groups, namely, resolving

parenchymal infiltrations, glandular calcifications and Ghon tubercles. The earliest and most extensive of the lesions characteristic of primary tuberculosis are represented by parenchymal infiltrations, of which 27 examples were discovered. In general these parenchymal lesions were relatively more frequent in the younger than in the older groups of children, and their combined incidence amounted to 4.7 per cent (Table 1) of the entire group of 579 positive Mantoux reactors. In each of these 27 children the parenchymal infiltrations have slowly resolved, although in every case many months were required before complete resolution was accomplished (See Figs. 1 and 2). Accompanying or following the final disappearance of these infiltrations calcium deposits have appeared, located usually within the related lymph nodes as well as in the area previously occupied by the infiltration. Later, in the majority of these children gradually increasing amounts of calcium appeared at sites of these foci, resulting eventually in the production either of calcified glands alone or of well-defined Ghon tubercles, associated with calcifications of the adjacent hilum nodes. The follow-up study of these cases at Lymanhurst has given us an opportunity to follow carefully all the various stages through which these extensive early primary parenchymal lesions pass, leading finally to their complete disappearance and replacement by calcified scars. Up to the present time I have had the privilege of observing 73 infants and children in whom lesions of this type were present. Two of these cases have been under observation for 9 months, a third for 28 months, and the remaining 68 cases have been watched for periods ranging from 3 to 9 years; and during this time no deaths have occurred in any of these 73 children. A few years ago we expected all of the cases having extensive parenchymal infiltrations to die soon of tuberculosis, particularly when the condition was found in young infants. Today we expect every case of this type to survive if protected thereafter from reinfection.

During the 11 years the follow-up study has been in progress at Lymanhurst not a single child has died of a primary tuberculosis. If deaths do result from primary infections by the tubercle bacillus, the experience at Lymanhurst indicates that such occurrences are rather rare during infancy and childhood. In most cases (all in our experience) extensive parenchymal lesions resolve and disappear leaving relatively inconspicuous calcified scars and, during the months this resolution is taking place, the patient, whether a young infant or an older child, may enjoy excellent health. At times severe and alarming symptoms are present for variable periods early in the course of the disease, following which a long period of symptomless convalescence ensues. This experience is very impressive in revealing the remarkably efficient power with which infants and children alike are endowed by Nature to overcome a primary tuberculous infection. As a result of past experience I feel that in the

dosage ordinarily received in human experience a single primary infection by the tubercle bacillus ordinarily fails to kill an infant or child who is in good health at the time the initial infection occurs.

The other lesions representative of the childhood type of tuberculosis included the glandular calcifications and Ghon tubercles, and among the 579 positive Mantoux children the incidence of the former (29.9 per cent, 173 cases) greatly exceeded that of the latter (11.6 per cent, 67 cases, Table 1). Of infected children, therefore, the data indicated that the calcified intrathoracic lymph nodes occur much more commonly than do Ghon tubercles. These calcified scars in general are relatively old lesions typical of primary tuberculous infections which occurred months and years ago, whereas their precursors, the resolving parenchymal infiltrations, are comparatively early and fresh lesions. Regardless of the marked difference existing in their appearance on the Roentgen ray film, these early and later lesions merely represent different stages in the evolution of primary tuberculosis as it commonly occurs in the human lung, and collectively they constitute the complete Roentgen ray picture of the clinical condition spoken of as the childhood type of pulmonary tuberculosis.

In this study 13 children were found who had consumption. The diagnosis of the adult type of tuberculosis was made in these cases after repeated Roentgen ray examinations, which revealed mottled subapical lesions which later tended to spread and to form cavities. At the Lymanhurst School only cases of primary tuberculosis are admitted, so these 13 children were transferred either to hospitals or to sanitoriums for further treatment, and in this group of cases the mortality has been high. The adult type of tuberculosis has developed in certain of these children, postdating several years the known presence of scars due to primary tuberculosis. This is illustrated by the case whose Roentgen ray films taken in 1921 and 1932 are shown in Figs. 3 and 4. Eleven years ago this boy had a positive tuberculin reaction, and on Roentgen ray examination (Fig. 3) marked calcification was found in the hilum glands on the right side, identifying the location of his primary tuberculosis. Eleven years later his Roentgen ray films (Fig. 4) show an extensive mottled tuberculous infiltration of the opposite lung and a small lesion in the periphery of the right lung. At this time, however, the calcified glands discovered long ago show no tendency toward breaking down, thus there is no Roentgen ray evidence that his phthisis resulted from a lighting up of the old infection acquired 11 or more years previously. In this case his consumption is confined almost exclusively to the lung opposite to that in which the primary focus is located, and an illogical stretch of the imagination is required to suggest that this lesion on the left resulted from a lighting up of this old lesion on the right, rather than being caused by an exogenous reinfection. Other cases similar to this have been observed at

Lymanhurst, in which as Roentgen ray films are taken year after year: new lesions have appeared postdating the known presence and location of older primary tuberculous foci, developing as frequently in the opposite as in the same lung in which the calcified primary lesion was located. Neither at the time of the appearance of these new infiltrations, nor later, has any case been discovered in which the Roentgen ray examination revealed evidence of a reactivation of the previously existing old calcified scars of primary tuberculosis. Furthermore, these old calcified scars have remained unchanged throughout the entire course of the subsequently developed consumption. On Roentgen ray examination immediately before death ensues they still appeared to be as quiescent as they were before the adult type of tuberculosis developed. This failure to find evidence of consumption resulting from a breaking down of calcified lesions of primary tuberculosis suggests that phthisis does not result from a reactivation of an infection acquired in childhood, but develops rather following a reinfection (received in sufficient dosage to produce a parenchymal lesion) of an individual whose body already harbors a focus of primary tuberculosis. This implies that an initial infection by the tubercle bacillus alters the immune reaction of the human body in such manner that the soil is prepared for the development of the adult and killing type of tuberculosis in these individuals when reinfections later occur in sufficient dosage to produce parenchymal infiltration in the lungs. To date we have not seen phthisis develop following a primary tuberculous infection in any child who was known to have a negative Mantoux test previous to the time the initial infection took place. Following such an experience these children uniformly develop the benign type of tuberculosis which eventually calcifies. In children in whom the Mantoux test was known to be positive and who had calcified scars of primary tuberculosis, we have not seen the benign childhood type of tuberculosis develop a second time. In our experience the human body can reduce an infection into what is known as a primary complex only once, and if these individuals later develop additional tuberculous lesions these new infiltrations are always of the type characteristic of phthisis. In this connection it is interesting to note that von Behring[50] held that phthisis resulted from a reinfection of a person infected with the bacillus during childhood. Orth[51] has furnished pathologic evidence that old lesions need not show evidence of recent activity, and that acute tuberculous reinfection may supplant a quiescent one and cause death. Bachmeister[52] could produce typical apical phthisis in rabbits only when a previous tuberculous infection had occurred somewhere in the animal. He concludes that for the production of typical phthisis a relative immunity of the body is necessary, and this is produced by an early primary infection. On careful postmortem examination Opie[53] found that apical tuberculosis in the lung of adults is always

accompanied by evidence of coexisting focal tuberculous infection of the childhood type. In cases of active pulmonary tuberculosis he always finds evidence of preceding tuberculous infection. The possibility of an interrelationship existing between the appearance of sexual maturity and the development of consumption following reinfection of previously infected children is suggested by the tendency for the adult type of tuberculosis to make its appearance during the teens. It was during this period of childhood exclusively that the 13 cases of the adult type of tuberculosis were found in this series of 579 infected children. On the basis of the findings in this group of cases combined with a larger experience of over 9000 children examined at Lymanhurst during the past 11 years, the following outline is offered as representing the conception this experience has given with regard to the evolution of tuberculosis in the human lung.

Summary. 1. Primary tuberculous infections of the lungs are revealed by the Roentgen ray films as parenchymal infiltrations, calcified glands and Ghon tubercles.

2. These lesions although varied in appearance merely represent different stages in the development of one and the same clinical condition, namely primary tuberculosis, or tuberculosis of the childhood type.

3. The general tendency for lesions resulting from an initial infection by the tubercle bacillus is first to resolve and later to calcify.

4. The human body can resolve a tuberculous infection into what is known as the primary complex only once.

5. When once reduced to calcified scars these primary tuberculous lesions do not become reactivated later in the production of the adult type of tuberculosis (consumption).

6. Death seldom and possibly never results from a single primary pulmonary tuberculous infection. The prognosis is excellent in infancy as well as in later childhood, provided reinfection is prevented.

7. Primary tuberculous infections of the lung, if extensive, produce symptoms of varying severity, which subside in the course of a few to several weeks. Thereafter, throughout the remainder of the life of the patient these primary lesions produce no clinical symptoms. (Occasionally a very large Ghon tubercle acting as a foreign body may erode a bloodvessel and cause hemoptysis, and in rare instances may be expelled from the lung in coughing.)

8. Consumption (phthisis) does not develop as a result of an initial infection by the tubercle bacillus. The first infection occurring at any age in life uniformly resolves and calcifies.

9. Consumption develops following a reinfection of individuals who previously have had a primary infection.

10. The reinfections responsible for the development of phthisis are probably exogenous in origin in the majority of cases.

11. The lesions of reinfection (adult type of tuberculosis or phthisis) usually appear in the subapical portions of the lungs.

12. These lesions may be present for months and years, without producing symptoms, physical findings or showing any tendency to spread.

13. During the teens previously dormant lesions characteristic of the adult type of tuberculosis frequently tend to spread, to produce cavities and to cause death.

14. The adult type of tuberculosis seldom calcifies.

15. Puberty seems to favor the breaking down of previously existing apparently quiescent subapical infiltrations of the adult type of tuberculosis. Primary infections occurring during puberty, however, behave much the same as do similar infections taking place in infancy and early childhood.

16. Lesions of the adult type of tuberculosis tend to spread and cavitate, whereas infiltrations resulting from initial tuberculous infections tend to recede and calcify.

17. The prognosis is grave for the adult type of tuberculosis. This type of the disease frequently results in death, whereas primary infections are seldom fatal.

18. The relationship existing between the childhood and the adult type of tuberculosis seems to consist largely in the tendency for the primary infection to prepare the patient for the development of phthisis should he perchance later experience a reinfection of sufficient severity to produce an intrapulmonary lesion.

19. Phthisis apparently does not customarily result from a lighting up of an old infection received in childhood.

20. The part that the former childhood infection seems to play in favoring the later development of phthisis seems to depend more upon the changes which this primary infection caused with respect to the manner in which the body reacts thereafter to the tubercle bacillus and its products, rather than upon a lighting-up of the old disease acquired during childhood.

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INTESTINAL OBSTRUCTION CAUSED BY FOOD.

CASE REPORT.

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In a recent report Elliott reviewed the literature on intestinal obstruction caused by food and found 39 cases of this type which had been reported since 1910. Of these cases the diagnosis was confirmed by operation or necropsy in 26 instances, while of the others the diagnosis was doubtful in 5 cases. Of the food material which caused obstruction, orange pulp was the cause in only 1 case,

to which Elliott added his own case which was also caused by this fruit. He states that his case is the first of this kind, proved by operation and necropsy, to be reported in this country. At the time of the appearance of this article I had under my care in the Jewish Hospital a typical case of acute intestinal obstruction which was caused by orange pulp and which might be of interest to record.

Case Reports. A white female, aged 57 years, was admitted on June 27, 1932, at 9.20 P.M., complaining of severe abdominal pain, intermittent in character, and repeated attacks of vomiting. She had been in good health until the day before admission when she developed crampy pain in the midabdomen, which gradually became more severe and was unrelieved by sedatives. An enema which had been given was returned without either feces or gas. Her temperature was 100.4° F., pulse 90 and respirations 22. Her previous medical history was significant only in that she had once had pneumonia and also that she had never had any abdominal operation. Physical examination revealed a short, stout type of individual, the abdominal fat preventing a very satisfactory examination for the presence of masses, but no rigidity was noted. The condition was typical of acute intestinal obstruction of undetermined origin, although on account of her age a carcinoma of the bowel was considered most probable.

Immediate operation was done under ether anesthesia through a lower midline incision. On opening the peritoneal cavity a moderate quantity of clear peritoneal fluid escaped and an examination of the entire colon revealed nothing abnormal. The lower ileum contained a mass between 2 and 3 inches long which felt boggy and completely obstructed the bowel at this point. Although the mass could not be moved very far, it was evident that it was in the lumen and not in the wall of the bowel. An enterostomy was done and a mass of yellow vegetable material was pushed from the bowel. A rubber catheter was sutured into the enterostomy and the abdomen was closed without further drainage. Examination of the specimen after the operation showed that it greatly resembled inspissated sweet potato, but a closer inspection revealed that it was composed of two sections of orange which had become impacted side by side. Positive identification was made by finding a few orange seeds inside the mass and on questioning the patient after the operation she stated that she had eaten oranges about 12 hours before the onset of her pain. Because she had no teeth she swallowed the sections of orange without careful mastication.

After operation all of her abdominal symptoms subsided very promptly. The next day she showed signs of pulmonary trouble which later developed into a bilateral pneumonia and in spite of strenuous efforts at treatment, including continuous use of an oxygen tent, she died on July 7, 1932, 10 days after the operation.

The above case presents most of the features which Elliott found in his review, such as: (1) An edentulous patient; (2) short interval (12 hours) between ingestion of the orange and the onset of obstruction; (3) the site of obstruction was in the lower ileum; (4) failure of accurate diagnosis of the cause of the obstruction; (5) fatal termination following operation, although death was due to postoperative pneumonia as the obstruction had been entirely relieved.

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THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE.

A STUDY OF 235 CASES OF NONHEMOLYTIC JAUNDICE DUE TO CARCINOMA, CALCULUS IN THE COMMON BILE DUCT AND LIVER DEGENERATION.

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THE recognition of diseases in which jaundice is the chief sign is in many instances a difficult diagnostic problem. Numerous laboratory tests for liver function and aids in the diagnosis of biliary tract disease have been developed in the past 20 years, but their application to the differential diagnosis of the causes of nonhemolytic jaundice has been disappointing. For this reason, we have reviewed a number of such cases seen in the Presbyterian Hospital in recent years to ascertain whether any clinical data other than that which is generally appreciated could be found to aid in differential diagnosis.

Cases of nonhemolytic jaundice, where the jaundice is one of the outstanding complaints may, in the main, be divided into three groups to which we have largely confined our attention: (1) So-called catarrhal jaundice and atrophy of the liver (*i. e.*, idiopathic acute yellow atrophy, poisoning by arsphenamin and cinchophen); (2) carcinoma involving the pancreas, bile ducts or gall bladder and primary carcinoma of the liver; (3) cases with calculus in the common bile duct. Other causes for nonhemolytic jaundice were not included in this study, either because they were uncommon or because, as in Laennec's cirrhosis, the diagnosis usually offers less difficulty.

All the cases of jaundice due to either neoplasm or calculus in the common bile duct were proven either by operation or by autopsy. The cases of catarrhal jaundice were not proven by these two methods, but all ran the usual course of that disease and were followed to the complete disappearance of their symptoms and often

much longer. Most of the cases of acute yellow atrophy came to autopsy and the rest presented the typical symptom complex of that condition.

The following table gives the number of cases included in this series:

CASES OF JAUNDICE STUDIED.

	Cases.
Group I:	
Catarrhal jaundice	81
Arsenic poisoning	15
Acute yellow atrophy	17
Group II:	
Carcinoma of pancreas	30
Carcinoma of bile duct	9
Carcinoma of gall bladder	10
Primary carcinoma of liver	7
Group III:	
Calculus in common bile duct	66
Total	235

Results of Analysis of Cases. *Age.* Age is of considerable importance in differential diagnosis. Pronounced icterus in younger individuals is usually due to what is known as catarrhal jaundice. Of the patients with catarrhal jaundice and acute yellow atrophy 80 per cent were below the age of 40 years. The youngest patient with acute yellow atrophy was 29 years of age, and in general it may be said that the older the patient with signs suggesting catarrhal jaundice, the more likelihood there is of the condition progressing to atrophy of the liver.

In contrast with the catarrhal jaundice group, over 80 per cent of the patients with either calculus in the common duct or carcinoma with jaundice were over the age of 40 years. The cases of arsphenamin jaundice occurred in the same age groups as did those of carcinoma and stone in the common duct, being evenly distributed through the decades after the age of 30 years.

Sex. Sex distribution merely confirmed the figures frequently reported. There was a slight predominance of males in the catarrhal jaundice group and of females in the acute yellow atrophy group. In the carcinoma group, however, sex is of more significance. In the carcinoma of the gall bladder group 71 per cent of the patients were females and most of those with primary carcinoma of the liver were males. Carcinoma of the bile duct was slightly more common in males than in females. Of the patients with calculus in the common bile duct 71 per cent were females.

Degree of Jaundice on Admission. Patients with carcinoma of the pancreas, gall bladder or bile duct usually presented a moderate or intense degree of jaundice when first seen. In primary carcinoma of the liver the jaundice was slight, if present at all. In patients with calculus in the common bile duct the degree of jaundice on admission to the hospital was extremely variable—approximately equal numbers presenting a jaundice which was described as slight, moderate or intense. This was also true of the cases of catarrhal jaundice and necrosis of the liver.

Duration of Jaundice on Admission. In the patients with catarrhal jaundice and acute yellow atrophy the jaundice had existed in the majority of instances less than 2 weeks. In the carcinoma group, on the other hand, the patients had usually noticed the presence of jaundice at least a month before entry and in some cases much longer.

In the patients with calculus in the common bile duct the duration was quite variable. Many patients described it as intermittent or varying in

intensity. These features were very seldom mentioned by any of the patients who had carcinoma or catarrhal jaundice. Many of the patients with stone in the common duct gave a history of a previous attack of jaundice and a fair proportion of them were first seen at a time when the jaundice was subsiding. The presence of any of these features in the history of a patient with jaundice weighs heavily against carcinoma and in favor of stone in the common duct.

Initial Symptoms. The initial symptom in catarrhal jaundice and liver necrosis was extremely variable but interesting in comparison with the other two groups. It was most commonly nausea or vomiting but frequently malaise, jaundice, epigastric pain or anorexia. One case had a chill at onset.

In the group with carcinoma approximately one-half of the patients gave pain in the upper abdomen as the first symptom. The next most common initial symptom was jaundice and in a small percentage of cases the first indication of illness was weakness or pruritus. Abdominal pain was the chief initial symptom in individuals with stone in the common duct. A few patients mentioned fever, rigor or jaundice as their first complaints.

Abdominal Pain. The incidence of pain in the three groups of patients is of considerable interest from the standpoint of diagnosis. Some type of abdominal pain or discomfort was present in the majority of cases in all the groups.

Slightly more than one-half of the patients with catarrhal jaundice and necrosis of the liver complained of some type of upper abdominal distress. This varied from sharp pain to vague discomfort—a greater number complaining of the latter.

Pain was present in the majority of cases in all of the types of carcinoma. That it is the most frequent initial symptom of that condition has already been mentioned. Of the entire group of patients with carcinoma 65 per cent had pain. In carcinoma of the pancreas or bile ducts it was apt to be a persistent and boring epigastric pain. In carcinoma of the gall bladder it was frequently sharp and cramp-like. The pain in primary carcinoma of the liver is occasionally sharp but more frequently dull.

In the patients with calculus in the common bile duct, pain was the most important diagnostic sign. It was characteristically severe and cramp-like, located in the epigastrium or in the right upper quadrant and in the majority of cases radiated to the back or shoulder. Two of the 66 patients with stone in the common duct gave no history of pain, causing diagnostic uncertainty until exploration.

Pruritus. In catarrhal jaundice and atrophy of the liver itching is mild when present. In our group it was present in only one-fifth of the cases. On the other hand, nearly all of the patients with carcinoma of the pancreas, gall-bladder or bile duct complained of moderate or severe itching. Itching was usually absent in primary carcinoma of the liver. It was also absent in two-thirds of the patients with calculus in the common duct and variable in degree when present.

Weight Loss on Admission. A history of loss of weight on entry into the hospital was unusual in the catarrhal jaundice and liver necrosis group and common in the other two groups, median for weight lost in each of these being at 20 pounds. The essential difference between these two groups, however, was the fact that in the carcinoma group there was a recent progressive weight loss, whereas in the group with calculus in the common duct the loss of weight was usually intermittent, protracted and associated with frequent digestive disturbances.

Other Symptoms. Weakness as a prominent symptom is worthy of note, for it was an outstanding complaint in practically all of the patients with

carcinoma. It was uncommon in the catarrhal jaundice or stone in the common duct groups, but frequently present in patients who later showed signs of acute yellow atrophy. In 21 cases of catarrhal jaundice (25 per cent) there was a history of upper respiratory infection at the onset, whereas such a history was rare in the other groups.

Fever. The majority of the patients with catarrhal jaundice and liver necrosis ran a temperature which exceeded 100° F. and in a few instances reached 102° and 104°. On the other hand, in carcinoma of the pancreas with jaundice, fever was rarely present, there being only 1 individual in the group with a temperature of more than 100° F. by rectum before operation. In the other types of carcinoma producing jaundice, fever was a common occurrence. Likewise, in the cases with calculus in the common bile duct fever was usually present.

Tenderness in the Upper Abdomen. Tenderness over the liver was present in over one-half of the cases of catarrhal jaundice and necrosis of the liver, and in one-third of the patients with stone in the common duct. It was absent in the group with carcinoma.

Liver Size. In jaundice due to carcinoma the liver was found to be enlarged in most cases on admission to the hospital. This applies to all of the types of carcinoma considered here.

It is difficult to speak categorically of the size of the liver in catarrhal jaundice and liver necrosis from the data at hand, as the patients were not all seen at the same stage of the disease. In reviewing the individual cases, however, the impression is confirmed that the liver usually increases in size early in the disease and may be felt 2 to 4 cm. below the costal margin in the right midclavicular line. Later, it recedes to or beneath the costal margin. This shrinkage of the liver in the later stages of the disease, associated at times with a marked diminution of the liver dullness, is the event which gives cause for alarm, except when this change is noted during convalescence. When there is persistent vomiting increasing jaundice and bile remains absent from the stools in patients who are thought to have catarrhal jaundice, progressive atrophy of the liver may be suspected. In the group of patients with calculus in the common bile duct the liver was usually found to be enlarged.

Enlargement of the Spleen. The presence of a palpable spleen is a definite aid to diagnosis. It was considered to be enlarged on admission in 19 (26 per cent) of 66 cases of catarrhal jaundice. It was palpable in a corresponding proportion of the cases with arsenic necrosis of the liver and acute yellow atrophy.

In carcinoma of the pancreas the spleen was found to be enlarged in only 2 cases. One of these patients also had myeloid leukemia and the other had marked biliary cirrhosis. The latter case is of interest in that the splenomegaly and also a positive Wassermann test led to the erroneous pre-operative diagnosis of syphilis of the liver.

The spleen was enlarged in only 1 patient in the group with calculus in the common duct. This patient had developed a terminal septicemia and was found to have a large acute splenic tumor at autopsy.

Gall Bladder Size. Palpation of the gall bladder when compared with the operative findings was shown to be rather inaccurate. In the majority of the cases of carcinoma of the pancreas, bile duct and gall bladder, enlargement of the gall bladder was demonstrated at operation, although in over one-half of these cases it had not been recognized on examination of the patient.

It was of interest to find that one-fourth of the patients with calculus in the common bile duct had enlargement of the gall bladder at operation. This was usually associated with a chronic cholecystitis. In most of these cases the gall bladder had been accurately palpated before exploration.

In the catarrhal jaundice group there were 2 patients in whom the gall bladder was thought to be enlarged on physical examination. This led to the diagnosis of carcinoma of the pancreas, which was later shown to be erroneous when the patients' symptoms disappeared completely.

Ascites. Ascites was uncommon in the cases studied. It occurred late in a number of cases of acute yellow atrophy. It was present in 6 of the 7 cases of primary carcinoma of the liver and in 1 case of carcinoma of the pancreas. Ascites in these instances was usually associated with a concomitant hepatic cirrhosis. It was absent in the group with calculus in the common duct, except in 1 patient who also had Laennec's cirrhosis.

Diabetes. An additional aid in the diagnosis of carcinoma of the pancreas with jaundice is the presence of diabetes mellitus. Seven of the 30 cases in this series had a persistent glycosuria. Furthermore, the onset of the symptoms of diabetes in a few cases seemed to coincide with the development of the carcinoma.

"Amin Breath." The peculiar pungent odor of the breath frequently detected in acute yellow atrophy was rarely mentioned in the records. It is not usually observed early in the disease and is of little help in early diagnosis. Its presence was mentioned in 9 of 16 cases in this series and also in 1 case of arsenic poisoning with jaundice. Subsequent experience has suggested that, if it had been sought for, it might have been noted frequently in the more severe cases of catarrhal jaundice. There was no mention of "amin breath" in the records of patients with stone in the common duct or carcinoma.

Additional Signs. A number of other significant signs in these cases deserve comment. Some form of hemorrhage was observed 3 times in severe catarrhal jaundice and 10 times in acute yellow atrophy. The presence of a rash may aid in confirming the diagnosis of acute yellow atrophy or catarrhal jaundice. The rash when present is usually acneform, although in 2 cases it was erythematous.

The presence of edema, of neurologic signs, or low blood urea or uric acid and high blood amino acids occurring late in the course of acute yellow atrophy is of no aid in early diagnosis.

Stool Bile on Admission. One of the mainstays in the differential diagnosis of jaundice is the mercuric chlorid test for urobilin in the stool. In our series this test was found to be of most significance in the diagnosis of carcinoma of the pancreas, for in almost every case it was negative. This test was also negative in all but 1 of the cases of carcinoma of the gall bladder or bile duct. It was always positive in primary carcinoma of the liver.

The results were by no means so uniform in the group with calculus in the common duct. In only 40 per cent of those cases in which the test was reported was it negative. The mercuric chlorid test was negative in approximately the same percentage of those patients who had catarrhal jaundice and liver necrosis. It can, therefore, be of no help in differentiating the latter group from the cases with calculus.

Erythrocyte Count. The red blood count is generally of little aid in the differential diagnosis of the types of jaundice considered here. Anemia was slight when present in the patients with carcinoma.

Leukocyte Count. Leukocytosis of some degree was found in a considerable number of cases in all of the three groups. In the catarrhal jaundice and liver necrosis group the white count exceeded 10,000 per c.mm. in one-fourth of the cases. A slightly larger proportion of the cases of carcinoma with jaundice presented some degree of leukocytosis.

Serum Bilirubin. The serum bilirubin was not determined in the majority of instances. From the figures obtained, however, it appears that the highest values tend to occur in catarrhal jaundice and acute yellow atrophy. Serum bilirubin values which exceed 25 mg. per cent usuall-

indicate liver degeneration. Experience with the van den Bergh reaction leads us to believe that it is useful in differentiating hemolytic from nonhemolytic jaundice, but that it is of no aid in differentiating between the types of jaundice which are considered in this study.

Analysis of Errors in Diagnosis. Errors in diagnosis were most frequent in the group of patients with carcinoma. In many instances various clinical opinions included all of the chief causes of nonhemolytic jaundice. Some of the patients with carcinoma were regarded as having cholelithiasis. This error appears to have been dependent upon the history of epigastric pain in these cases. It has already been emphasized that epigastric pain is an early and prominent symptom in carcinoma. Another error frequently made in the diagnosis of carcinoma was attributable to the coincidental presence of a positive blood Wassermann test. The latter finding often led to a diagnosis of syphilis of the liver, in spite of the fact that a positive Wassermann test in the presence of jaundice is always open to doubt. Syphilis of the liver as a cause of jaundice in the adult has been a very uncommon finding in the cases studied in this hospital for the past 10 years.

There were very few errors in the diagnosis of cases with jaundice due to stone in the common duct. In this group the suggestive character of the pain, the sudden onset of the symptoms, the frequent presence of right upper quadrant tenderness and leukocytosis usually suggested the nature of the underlying process.

Errors in diagnosis were relatively frequent in the catarrhal jaundice group. The patient was often suspected of having carcinoma. The main reasons for such an error appear to have been: (1) Advanced age of the patient; (2) a history of weight loss; (3) the apparent presence of an enlarged gall bladder. These features in themselves might be expected to lead to diagnostic errors, but in these cases other findings should have argued strongly against neoplasm. Several cases of acute yellow atrophy were incorrectly diagnosed for similar reasons.

If there are several factors concerned in the production of the disease picture, such as coincident calculus in the gall bladder and carcinoma, the opportunities for error in diagnosis are greatly increased.

In summary, the outstanding causes for error in the diagnosis of the cases of jaundice in this series were: (1) The high incidence of pain in carcinoma with jaundice; (2) positive Wassermann test; (3) erroneous palpation of the gall bladder.

Differential Diagnosis. It is not practicable to differentiate clinically early in the disease between cases with catarrhal jaundice and cases which are to develop acute yellow atrophy. In fact, the early clinical pictures in these conditions seem to be identical. The symptoms and signs in necrosis of the liver due to some drug, such as arsphenamin or cinchophen, are the same as those seen in catarrhal jaundice or acute yellow atrophy, with the exception that patients with the latter conditions may give a history of antecedent upper respiratory infection. Where the history of the exhibition of such a drug can be obtained, however, the diagnosis of liver necrosis or "toxic hepatitis" is facilitated.

The diagnosis of catarrhal jaundice in the middle-aged individuals may be difficult. Of particular assistance in making this diagnosis may be: (1) The usual short duration of the jaundice at the time when the patient feels sick enough to present himself for examination; (2) the usual vagueness of the presenting symptoms, namely,

a moderate degree of dull epigastric pain, malaise, anorexia and nausea or vomiting. Weakness is not an outstanding complaint in these cases, as it is in carcinoma, and there is seldom a history of antecedent loss of weight. Itching is usually absent, and if present it is slight. When the spleen can be felt it is an important aid in diagnosis. Tenderness over the liver is present in over one-half of the cases. Minor signs which may be of assistance are the "amin breath" and an acneform eruption. A very high serum bilirubin favors the diagnosis of catarrhal jaundice or acute yellow atrophy rather than carcinoma or calculus.

Calculus in the common bile duct offers few difficulties in diagnosis when there is a history of one or more attacks of the characteristic pain with local tenderness and leukocytosis. When the pain is absent, however, the diagnosis is difficult and such cases are apt to be regarded as carcinomatous. The very considerable loss of weight which may attend this condition may also be misleading.

TABLE 1.—SIGNS AND SYMPTOMS IN 235 CASES OF NONHEMOLYTIC JAUNDICE.

	I. Catarrhal jaundice, acute yellow atrophy, arsphenamin jaundice.	II. Carcinoma of pancreas, gall bladder, bile duct, liver (primary)	III. Calculus in common bile duct.
Age	80% under 40 years	80% over 40 years	80% over 40 years.
Sex	Catarrhal jaundice, 67% males; acute yellow atrophy, 76% females; arsphenamin jaundice, 53% females	Pancreas, 72% males; gall bladder, usually females; bile duct, evenly divided; liver, usually males	71% females.
Degree of jaundice on admission	Variable	Marked, except in primary carcinoma of liver	Variable.
Duration of jaundice on admission	Less than 2 weeks in 78%	More than 3 weeks in 65%	Often intermittent, recurrent or subsiding.
Chief initial symptom	Anorexia, nausea, vomiting or malaise, 60%	Pain, 48%; jaundice, 27%	Pain, 85%.
Upper abdominal pain or discomfort	Present in 56%	Present in 65%	Present in 97%.
Pruritus	Usually absent and mild when present	Almost always present except in primary carcinoma of liver	Variable.
Loss of weight	Usually none	Average, 20 pounds	Average, 20 pounds.
Asthenia	Usually absent	Usually present	Usually absent.
Prodromal upper respiratory infection	Present in 25%	None	None.
Fever	Usually present	Pancreas, usually absent; gall bladder, present; liver, present; bile duct, present	Present.
Upper abdominal tenderness	Present in 55%	Absent except in primary carcinoma of liver	Present in 29%.
Liver size	Enlarged early	Enlarged	Enlarged.
Spleen	Palpable in 25%	Not palpable	Not palpable.
Diabetes mellitus	Absent	Pancreas, present in 23%	
Acneform eruption	Often present	Absent	Absent.
Stool bile	Variable	Pancreas, gall bladder, bile duct, persistently negative; liver, positive	Variable.

The important features disclosed concerning carcinoma of the pancreas with jaundice are: First, that pain is the commonest initial symptom and is present early in the disease in the majority of cases. This pain is usually dull, boring and epigastric in location. Bile is usually absent from the stool and itching is almost always

present, which is true of neither catarrhal jaundice nor calculus in the common duct. When the patient is first seen the jaundice is usually intense. He gives a history of a considerable loss of weight and weakness is an outstanding complaint.

On physical examination the liver is enlarged but not tender and the spleen cannot be felt. Palpation of the gall bladder is at best a very deceptive physical sign, but in many instances it is found enlarged at operation. It must be remembered, however, that one-fourth of our cases of calculus in the common duct were also found to have enlarged gall bladders at operation. Fever is usually absent. The presence of diabetes mellitus, apparently of recent onset, may be of additional help in diagnosis.

In carcinoma of the bile duct or gall bladder the clinical picture is usually not very different from that seen in carcinoma of the pancreas and, in general, it is dangerous to hazard an opinion as to the exact location of a neoplasm obstructing the biliary tract. If, however, the patient is a female and gives a history of previous attacks suggestive of cholelithiasis and is running a fever, the palpation of a mass in the region of the gall bladder may suggest the diagnosis of carcinoma of the gall bladder.

Primary carcinoma of the liver should be suspected in a patient who shows evidence of cirrhosis of the liver, who gives a history suggestive of some type of neoplasm and who has fever, upper abdominal pain and jaundice of slight degree.

Conclusion. The records of 235 cases of nonhemolytic jaundice have been reviewed in order to determine what clinical evidence may be of assistance in differential diagnosis. The chief findings are summarized in Table 1.

THE INTERRELATION OF PERNICIOUS ANEMIA AND IDIOPATHIC HYPOCHROMIC ANEMIA.*

THE STUDY OF A FAMILY IN WHICH BOTH CONDITIONS OCCURRED SINGLY AND COMBINED.

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The medical literature reveals considerable evidence to prove an interrelationship between pernicious anemia and idiopathic hypochromic anemia. Disturbances of the gastrointestinal tract, typi-

* Presented at the Meeting of the American Society for Clinical Investigation held at Atlantic City on May 2, 1932.

fied by absence of free hydrochloric acid in the gastric juice, are closely linked with both diseases. The importance of this fact in relation to pernicious anemia has been shown by the now generally accepted work of Castle and his coworkers.[1] Recent reports on idiopathic hypochromic anemia with achlorhydria, by some called by other names—cryptogenetic achylic chloranemia,[2] simple achlorhydric anemia,[3] idiopathic hypochromemia[4]—have emphasized the association of achlorhydria with a hypochromic blood picture. The work of Mettier and Minot[5] has suggested that achlorhydria may alter the absorption or utilization of iron of the food in this disease.

Hypochromic anemia, as well as pernicious anemia, is found quite commonly in individuals with achlorhydria,[6,7,8,9] including those who have undergone operations upon the stomach.[10,11] Of especial significance are reports of hypochromic anemia developing in members of families in which pernicious anemia occurs.[3,12,13,14,15,16,17,18,19,20] Minot[21] has seen at least 10 such instances. Strauss[22] has observed 2 patients with marked hypochromic anemia associated with pregnancy whose mothers suffered from pernicious anemia. Achlorhydria in members of the families of pernicious anemia patients is well known. Wilkinson and Brockbank[19] collected from the literature 17 families in which 2 or more members had achlorhydria without pernicious anemia, 59 families in which pernicious anemia and achlorhydria existed in different members and 139 families in which 2 or more members were affected with pernicious anemia. Others[3,18,19,23,24,25,26,27,28,29] have reported and Minot[21] has observed pernicious anemia developing in patients who had previously been shown to have an idiopathic hypochromic anemia. Prior to 1872, Biermer[30] apparently had observed "chlorosis" preceding pernicious anemia. Patek remarked that "anemia of the secondary type has frequently been known to be a precursor of the primary form." Gram even postulated a stage in the development of pernicious anemia in which there may be a temporary simple anemia curable by iron.

It is a common experience in the treatment of pernicious anemia by liver therapy to observe a fall in color index as the red blood cell count rises—frequently to 0.7 and even less. If iron therapy is then introduced the hemoglobin may rise and the color index approach unity.[31] In this clinic there have been seen several striking examples of this "splitting" of response to therapy when material potent for pernicious anemia has first been administered and then iron following the subsidence of regenerative signs due to the effects of the potent material.[32] In pernicious anemia the tendency of the reticulocyte response to potent material to be smaller the lower the color index, as described by Minot and Heath,[33] may be explained if the prevalence of hypochromic, iron-responding anemia in patients with achlorhydria is born in mind.

It is reasonable, therefore, that the two conditions may coëxist.

Cases of anemia have been reported with a low color index, but a normal or increased cell size. These individuals, as Watkins,[34] Davies[9] and we[35] have observed, may respond in a degree to liver as well as to iron. However, this situation may occur in anemic states which undoubtedly are not related to Addisonian pernicious anemia; for example, anemia due to subacute blood loss and arising in pregnancy. A hypochromic blood picture in subacute combined degeneration of the cord has been observed.[3,23,36] Such a condition undoubtedly occurs occasionally, but these cases are probably instances of coëxistence of pernicious anemia and idiopathic hypochromic anemia. A megalocytic anemia is, of course, very much more apt to be present in untreated cases of this type.

A striking example of the interrelation of idiopathic hypochromic anemia and pernicious anemia is here presented. Observations are recorded on 10 individuals with the record of their unusual family history. The study brings up interesting additional problems, and suggests an attractive hypothesis concerning the etiology of such a combination. The opportunity to study this family is due to Dr. George R. Minot, who remembered investigating at the Massachusetts General Hospital in 1916 and 1917 2 sisters, each suffering from a puzzling type of anemia. They were not observed again until 1931, when they came to this clinic in response to inquiry. The family lived about 80 miles from Boston, which rendered the examinations necessarily infrequent and made it difficult to observe all members.

Methods. The blood cell counts were made with U. S. Bureau of Standards pipettes and counting chamber. The hemoglobin was determined by a Sahli hemometer which had been standardized by determinations of the oxygen capacity of the blood by the van Slyke method. One hundred per cent hemoglobin is taken as 15.6 gm. per 100 cc. or 21 volumes per cent oxygen capacity. The mean corpuscular volume[37] varied in normal individuals from 85 to 95 cu. micra. The tests of the fragility of the red blood corpuscles were made by adding to 1 cc. of varying concentrations of sodium chlorid solution 0.1 cc. of a 20 per cent suspension of washed corpuscles. The average extremes of beginning hemolysis and complete hemolysis in normal blood were respectively 0.48 and 0.27 per cent sodium chlorid. In performing the gastric analyses, 50 to 100 cc. of 7 per cent alcohol was first given, and if no free hydrochloric acid was present in 40 minutes histamin was injected subcutaneously and the contents examined every 20 minutes for 1 hour afterward.

Family History. Each member of the first generation of this family was born in Scotland. Little is known about their ancestors, but there was no knowledge that any had suffered from anemia or "nerve disease." The family relationship and summary of findings is shown in Table 1.

First Generation. The mother died at 73 years of age of "sugar diabetes." She had a stroke in 1923, living only 6 months thereafter. As a younger woman she was known to complain of a sore mouth, but she was always strong and well. It was never known that she had any trouble with her blood. She raised 10 children and had no difficulties with the pregnancies. However, all her life she had "terrible headaches" nearly

every week, generally unilateral. Her mother died at 57 years of age, cause unknown, and her father died at 79 years of age, of "old age."

TABLE 1.—SUMMARY OF THE IMPORTANT FINDINGS IN MEMBERS OF THE FAMILY.

Generation	I.	II.										III.				
Sex	♀	♂	♀	♂	♀	♂	♂	♀	♂	♀	♀	♀	♀	♂	♂	♀
Age	...	...	59	55	53	52	50	...	...	42	41	35	28	26	23	21
Anemia	..	..	+	0	+	Sl.	..	+	..	+	..	+	Sl.	0	0	0
Megalocytosis	..	..	(+)	+	+	+	..	+	..	+	..	..	0	+	+	0
Microcytosis	..	..	+	..	+	..	..	+	..	+	..	+	0	..	..	0
Fragility, r.b.c.	..	..	+	N	+	N	..	..	..	+	..	+	N	N	N	N
Gastric juice HCl	..	..	0	–	0	0	..	..	..	0	..	–	N	N	N	N
Diarrhea	..	..	+	+	0	0	..	0	..	0	..	0	0	0	0	0
Menorrhagia	0	..	+	..	+	..	..	..	..	0	..	+	0	..	..	0
Migraine	+	..	+	+	0	0	..	..	..	0	..	0	0	+	0	0
Easy bruising	..	..	+	0	+	0	..	+	..	+	..	+	0	0	0	0
Thyroid gland	..	..	+	N	+	N	..	..	..	+	..	(N)	+	N	+	N
History of cholecystitis	..	..	+	0	0	0	..	..	..	0	..	0	+	0	0	0
Restricted diet	..	..	+	+	+	0	..	..	..	+	..	0	0	0	0	+
Atrophy tongue	"Sore mouth"	..	+	0	+	0	..	..	..	+	..	0	0	0	0	0
Combined system disease	..	..	+	0	+	(0)	..	..	..	+	..	0	0	0	0	0
Dystrophy, nails	..	..	+	0	0	0	..	..	..	+	..	+	Sl.	0	0	0
Splenomegaly	..	..	+	0	+	0	..	..	..	0	..	0	0	..	0	0
Age at death	73	29	59	..	..	..	..	35	40	..	..	..	..	..	..	..
Remarks	"Diabetic stroke"	"Pneumonia"	"Shock"				"Perfect health"	Anemia	Tb. "hemorrhages"		"Good health"	Obesity	"Tired," "pale," ... attacks			

The father, aged 81 years, was living and well. He had always been robust and never anemic. His mother died at about 73 years of age, in Scotland, cause unknown. His father died between 40 and 50 years of age, in Scotland, cause unknown.

Second Generation. There were 10 brothers and sisters of the second generation, 5 of whom have been examined.

Andrew M., the first member of the second generation, died at 29 years of age of an acute "pneumonia." Before that he was troubled with "asthma." He was never pale.

Elizabeth M., the second member of the second generation, aged 59 years, was first seen at the Massachusetts General Hospital, in 1916, at the age of 45 years. She gave a history of menorrhagia commencing 1 year previously and coincidentally progressive symptoms of anemia. Physical examination revealed a moderately enlarged heart, palpable spleen and normal reflexes. Eye examination showed "vascular disease with an occasional hemorrhage." Blood examination: Red blood cells, 3,000,000 per c.mm.; hemoglobin, 43 per cent (Sahli); "marked anisocytosis and poikilocytosis, some red cells, very fat, others mere shadows;" achromia was pronounced; white blood cells, 5400 per c.mm.; neutrophils, 61 per cent; small lymphocytes, 32; large lymphocytes, 7. Blood platelets markedly increased. Fragility test showed hemolysis commencing at 0.45 per cent and complete at 0.18 per cent sodium chlorid solution. Pathologic report of uterine curettings: "Hyperplastic endometritis. Endocervicitis."

Following this she improved, but she was seen 1 year later with a recurrence of symptoms of anemia. There were no tongue symptoms or paresthesias. The sclerae showed jaundice. The spleen was palpable and reflexes normal. A tendency to ecchymoses was noted, as, for example, when venipuncture was done, and petechiae of the eyelids developed when a stomach tube was passed. Blood examination: Red blood cells, 3,080,000 per c.mm.; hemoglobin, 50 per cent (Tallqvist); white blood cells, 5400 per c.mm.; neutrophils, 48 per cent; small lymphocytes, 36; monocytes and large lymphocytes, 16; blood platelets normal. Normal bleeding and clotting time. Fragility test: Hemolysis began at 0.48 per cent and was not yet complete at 0.22 per cent sodium chlorid solution. Gastric analysis showed absent free hydrochloric acid. A transfusion of blood was given.

In 1922 her physician reported that the red blood cells were 3,000,000 per c.mm.; hemoglobin, 85 per cent; color index, 1.4. Dr. Minot examined the blood smear at this time and described it as typical of pernicious anemia.

I first saw this individual on February 27, 1931, when she gave the following additional history: Since girlhood she had suffered from menorrhagia, and about 40 years ago was in a hospital because of excessive flow. For 28 years, or since the birth of her sixth child, she had occasions, usually in January of each year, when she suffered from weakness, palpitation, dyspnea and often sore tongue and mouth. For about 15 years she had progressive difficulty in walking and suffered from paresthesias of the fingers and feet. Two years previously she was ill with right upper abdominal pain, jaundice and light-colored bowel movements. At this time she had a severe nosebleed. Menopause occurred 7 years previously, and she had no more flowing. For a year she had diarrhea 2 or 3 times a week. She had frequent headaches of a migraine type. Her diet for many years was very sparse in meat, but contained fruit and vegetables in moderate amounts. She drank 1 quart of milk and 4 cups of tea a day. The patient had been taking daily, for the past year, a potent liver extract derived from only 200 gm. of liver. Previous to this she had for years taken an "iron" medicine.

Marital history: She had been married 40 years; her husband was living and well; she had 6 children, ages 29 to 36 years, 5 girls and 1 boy. None of the female offspring had had menorrhagia or definite anemia except the second eldest (see Hazel M).

Physical examination, which was incomplete, showed a rather obese woman, plethoric, not icteric, with brown-gray hair and blue eyes. Tongue smooth, not atrophic, except at the edges. Moderate diffuse enlargement of the thyroid gland. Biceps, knee and ankle jerks were not obtained. Vibratory sense was absent over tibiae and malleoli. Abdomen was not examined.

Blood examination: Red blood cells, 4,320,000 per c.mm.; hemoglobin, 89 per cent; color index, 1.03. Red cells showed definite, not marked, abnormal variation in size and shape. No achromia. Mean corpuscular volume, 91 cu. micra (within normal limits). Icteric index, 2. Fragility test: Hemolysis commenced at 0.5 per cent, complete at 0.3 per cent sodium chlorid solution. White blood cells, 7000 per c.mm.; neutrophils, 67 per cent; lymphocytes, 19; monocytes, 6; eosinophils, 8. The neutrophils tended to be multinuclear. Blood platelets normal.

Unfortunately, this patient was not seen again because she died suddenly, 1.5 months later, of "cerebral hemorrhage."

Summary. This patient exhibited the following interesting features: Prolonged menorrhagia with, at times, spontaneous hemorrhages into the skin and from the nose; a hypochromic blood picture with achlorhydria 11 years ago; a megalocytic blood picture 9 years ago; splenomegaly; at

present evidence of combined system disease, diarrhea and some variation in size and shape of the red cells without anemia, following the ingestion for a year of a potent liver extract; occasionally increased resistance of erythrocytes; history suggestive of cholelithiasis; migraine; enlarged thyroid gland; a diet poor in meat, high in milk and tea. It is believed that she had pernicious anemia in a blood remission, combined system disease, and formerly hypochromic anemia associated with achlorhydria and a poor diet.

Allan M., the third member of the second generation, aged 55 years, was a wire weaver. His first wife died of childbirth. By this marriage he had a daughter who was married and had 2 children, 10 and 4 years of age. All 3 were said to be well. He had been married 15 years to his second wife, who was well except for "bronchitis." She had no pregnancies.

About 3 years previously he began to have attacks of diarrhea, occurring every 3 or 4 months, lasting several days. For about the same period of time he thought he had become somewhat pale and noticed some dyspnea and palpitation on exertion, and weakness. For about 10 years, 2 or 3 times a month, he had headaches, mostly right-sided, coming usually at the end of the week. He had no sore tongue, no numbness, paresthesias or difficulty in walking.

Five years ago he had his upper teeth extracted. His diet contained red meat about 4 days a week, but fruit seldom, and green vegetables only to the extent of a small helping a day. He had suffered from generalized discomfort in the abdomen 25 years ago and was told by his doctor that he had "hyperacidity." No gastric analysis was made. Otherwise he had always been well.

Physical examination: Somewhat pale, gray-black hair, light brown eyes, not jaundiced. Tongue coated, not atrophic. Lungs and heart not remarkable. Radial bloodvessels soft but tortuous. Blood pressure: systolic, 105; diastolic, 75. Reflexes normal. Vibratory sense over tibiæ present to a normal degree. Blood examination: Red blood cells, 4,715,000 per c.mm.; hemoglobin, 87 per cent. No increased variation in size and shape of the red cells. Mean corpuscular volume, 93 cu. micra. Fragility test: Hemolysis began at 0.48, complete at 0.28 per cent sodium chlorid solution. White blood cells, 6650 per c.mm.; neutrophils, 68 per cent; lymphocytes, 19; monocytes, 7.5; eosinophils, 4; basophils, 1.5. Blood platelets slightly increased. Gastric analysis showed only a trace of free hydrochloric acid 25 minutes after histamin, and no acid 50 minutes after histamin. Peptic activity of the gastric juice was normal.

A few weeks after he had been seen he developed severe diarrhea, with some bloody movements, and he required bed care for several weeks. He was seen again 4 months later when he had recovered from his diarrhea and had gained weight, but felt weak. Blood examination showed: Red blood cells, 4,400,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume, 101 cu. micra. The red cells seemed large but showed very little increased variation in size and shape. He had been on the same diet, and had taken no liver.

The noteworthy features of this case were the hypoacidity, history of diarrhea and migraine, and diet somewhat low in fruit and vegetables but containing appropriate amounts of protein and red meat. There was little, if any, anemia, but there was a definite slight megalocytosis.

Jessie S., the fourth member of the second generation, aged 53 years, was first seen at the Massachusetts General Hospital, April 5, 1916. She had been weak since the birth of her last child, 8 years previously, and since this time she had marked menorrhagia. There were exacerbations of weakness, and during one of these attacks she took Blaud's pills and felt improved for 1 year. Examination showed pallor, but no jaundice. The tongue was atrophic and clean. Roentgen ray examination of the chest

showed enlargement of the heart, especially of the right side. The liver was felt 6 cm., and the spleen 3 cm., below the costal margin. There was edema of both lower legs. The knee jerks were normal, there was no ankle clonus and Babinski sign was negative. Laboratory findings: Red blood cells, 2,080,000 per c.mm.; hemoglobin, 35 per cent (Sahli); the red cells were achromic, there was marked variation in size and shape and some polychromatophilia; white blood cells, 2250 per c.mm.; neutrophils, 74 per cent; lymphocytes, 23; "transitionals," 3. The blood platelets were decreased. The Wassermann test was negative. Coagulation time was normal. Fragility test: Hemolysis began in 0.5 per cent and was not complete in 0.22 per cent sodium chlorid solution.

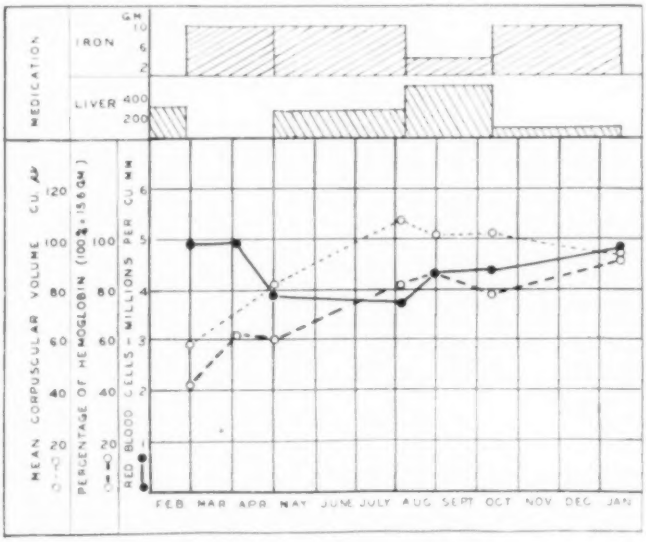

FIG. 1.—Changes in the blood of Jessie S. (See also Fig. 3.)

A dilatation and curettage was performed and she was sent home to rest. She took 45 grains of Blaud's pills a day for 3 months. Later she reported that she had had a year of good health, the best since her trouble began.

She was not seen again until February, 1931. The following is a summary of the findings: She stated that the weakness and pallor had continued and generally in January of each year she had palpitation, dyspnea and a smothered feeling in the chest. Menorrhagia had continued up to the menopause, 5 years previously, which was produced by a series of Roentgen ray treatments. She had occasional "canker sores" of the tongue. Within a few months she had had prickly sensations of the fingers and especially of her feet when she stood, interfering to a small extent with her walking. She thought her nails had always tended to break easily. She was constipated. Three years previously, at a time when she was very weak, she was given a transfusion of blood. After this she took daily liver extract, No. 343 (N. N. R.), derived from 600 gm. of liver, for 2 or 3 months and was much improved. Following this, she took smaller amounts of liver extract irregularly, but for the last 3 months she had been taking daily the extract derived from 200 to 400 gm. of liver. At about the time of the transfusion she had

a very severe nosebleed. Her diet for many years had contained fruit only once every other day, one helping of vegetables a day and small helpings of meat 4 times a week. She drank about 6 cups of tea a day.

She had been married 30 years. Her husband died in 1931 of an "acute Landry's paralysis." She had 3 sons, aged 29, 26 and 23 years. She thought all had been well but considered that the eldest son had always been pale. A blood examination of this son by his physician, on May 22, 1928, was as follows: Red blood cells, 4,000,000 per c.mm.; hemoglobin, 85 per cent; white blood cells, 7000 per c.mm. One made on February 12, 1931, was reported: Red blood cells, 5,240,000 per c.mm.; hemoglobin, 96 per cent; white blood cells, 8100 per c.mm., "normal smear." The other 2 sons are reported upon below.

Physical examination revealed a well-developed and nourished woman with white-gray hair and light blue eyes. Tongue smooth with complete atrophy of the epithelium of the tip and edges. No lymph node enlargement. Thyroid gland moderately enlarged. Heart moderately enlarged. Blood pressure was 115 systolic and 65 diastolic. Lungs negative. Spleen felt 3 cm. below the costal margin. Liver not palpable. Reflexes: biceps jerks present and equal, knee and ankle jerks not obtained. Babinski sign doubtful, no ankle clonus, definitely diminished vibratory sense over both lower extremities. The finger nails showed a moderate degree of koilonychia.

Laboratory findings: (The red blood cells and hemoglobin are recorded in Table 2.) White blood cells, 9200 per c.mm.; neutrophils, 61 per cent; lymphocytes, 29; monocytes, 6; eosinophils, 2; basophils, 2. Smear: 1 normoblast seen; red cells seemed, on the average, small and very achromic and to have marked variation in size and shape (Fig. 3, *a*). Blood platelets increased. Fragility test: Hemolysis began in 0.54 per cent and complete in 0.18 per cent. Icteric index, 3. Gastric analysis showed no free hydrochloric acid 1 hour after histamin subcutaneously and peptic activity was nearly absent.

TABLE 2.—CASE OF JESSIE S.

Date.	R.b.c., millions per c.mm.	Hemoglobin, per cent.	Mean corpuscular volume, cu. micra.	Liver, and liver extract, No. 343, derived from liver. Grams daily.	Iron and ammonium citrate. Grams of iron daily.
Feb. 27*	4.89	42	58	0	1.0
April 3	4.91	61	..	0	1.0†
May 16	3.92	60	82	200–300	1.0
Aug. 6	3.86	81	107	500	0.3
Aug. 27	4.31	87	101	500	0.3
Oct. 17	4.38	79	101	100	1.0
Jan. 16	4.82	92	97		

* Two to four hundred grams of liver had been taken for 3 months before observation but no iron.

† Omitted for 2 weeks.

Under the medication indicated in the table she gradually improved in strength and feeling of wellbeing. The paresthesias of the extremities, however, remained about the same. The fragility of the red cells approached normal, as the blood improved. The mean corpuscular volume rose above normal as large cells well filled with hemoglobin appeared in the circulation (Fig. 3, *b*) and later fell nearly to normal.

Of significance in this case are the prolonged history of anemia and menorrhagia, achlorhydria, symptoms and signs of mild combined system

disease, diet not very satisfactory, tongue atrophic, koilonychia and splenomegaly. Furthermore, of interest is the fact that a microcytic type of anemia was transformed during the course of iron therapy to a macrocytic type of anemia, and that improvement had occurred in the past on either iron or liver therapy.

James M., the fifth member of the second generation, aged 52 years, white, married, policeman, was seen on May 16, 1931, but was unable to remain for more than a very short time, and thus the examination was not thorough. He had always been well and strong except for an occasional "cold." He had had no serious illnesses nor headaches. His tongue had never been sore (except that he stated that certain foods had sometimes produced "cankers"); he had no indigestion or gas; his bowels moved once a day. He had noticed no easy bleeding or bruising or brittleness of his nails, no paresthesias. At about 18 years of age he was subject to nosebleeds.

Physical examination: He was an extremely well-developed man with rather plethoric complexion, sparse, gray hair and light blue eyes. The tongue was not atrophic, although the extreme tip was reddened. His finger nails were normally strong and convex.

Blood examination: Red blood cells, 4,120,000 per c.mm.; hemoglobin, 89 per cent. The red cells appeared large. Mean corpuscular volume, 108 cu. micra (normal extremes, 85 to 95 cu. micra). There was much greater variation in the size of the red cells than normal with only slight variation in shape. No achromia. Fragility test: Hemolysis began in 0.5 and not complete in 0.18 per cent. White blood cells, 6450 per c.mm. Differential: neutrophils, 57.5 per cent; eosinophils, 1.5; basophils, 0.5; lymphocytes, 33.5; monocytes, 7. Blood platelets normal. Icteric index, 8.

He was seen again about 1 year later, at which time he still felt well and strong. Although advised to eat liver he had taken scarcely any. He had noticed at times, during the previous 9 months, a little numbness of the tips of the fingers, and practically constant slight numbness of the toes which had gradually spread over both feet. He had had no sore tongue, no diarrhea and no weakness.

Physical examination at this time revealed almost the same findings as before with the following additions: the heart, lungs and abdomen were negative; the spleen was not palpable; knee jerks and ankle jerks were present, but there was complete absence of vibratory sense over the left tibia; there were no other demonstrable deep or superficial sensory changes; the gait was normal.

The blood examination at this time was similar to the previous one: Red blood cells, 3,450,000 per c.mm.; hemoglobin, 95 per cent; mean corpuscular volume, 105 cu. micra. There was considerable variation in size of the red blood cells. Gastric analysis revealed the complete absence of free hydrochloric acid after histamin.

The symptoms and signs of early combined system disease, the megalocytic blood picture and the gastric achlorhydria led to the diagnosis of pernicious anemia in the case of this man.

Archie M., the sixth member of the second generation, aged 50 years, was living and well, married and had no children. He was said to be "in perfect health."

Annie M., the seventh member of the second generation, died 12 years previously, at the age of 35 years. Two years before her death she gave birth to a son. She never felt well thereafter and her health gradually declined. She had pallor, breathlessness, palpitation and developed a "lemon yellow color" to the skin. She was bedridden 2 months before her death. One month before her death "big, purple blotches on the legs" were noticed. She never mentioned her tongue being sore. She tended to be constipated and was never known to have any diarrhea. She

evidently died of an anemia, of what kind it would be difficult to say, presumably pernicious anemia.

John M., the eighth member of the second generation, died, in 1925, at the age of 40 years, of pulmonary tuberculosis. He had many hemorrhages from the lungs. He was said to have "high color" at the times when he was well and was not having hemorrhages.

Gertrude M., the ninth member of the second generation, aged 42 years, housewife, was seen in February, 1931. She was in good health up to 6 years previously when her feet "went back on her." She had trouble with walking, paresthesias of the hands and feet, and at the same time her tongue, cheeks and throat became sore. The doctor, she thought, said that her "blood was 2,000,000" and he advised bed rest for about 6 weeks. At this time she noticed that she had black and blue spots on very slight injury. During the past 6 years, in or about January, she had become weak, pale and had some breathlessness on exertion and a constricting feeling in her upper chest. She also frequently had a sore tongue. She began taking raw liver 5 years previously and for the past 3 years she had taken daily "a third of a pound" of liver and also liver extract, No. 343 (N. N. R.), derived from 200 gm. of liver, with considerable benefit. She stated that "for years" her finger nails broke easily. She had no diarrhea. Catamenia occurred monthly, lasting 3 to 4 days, requiring 4 to 5 pads a a day. Her diet contained daily moderate amounts of fruit, vegetables and meat. For the past 6 years she ate red meat daily. Most of her life she took 8 cups of tea and 6 to 9 slices of bread a day.

She was married 21 years. Her husband was living and well, and her only child, a daughter, aged 20 years, was well, had no anemia and no disturbance of the menses. (See later, case of Ruth M.) The remainder of the history was negative.

Physical examination revealed a well developed and nourished woman, not obviously pale, with gray eyes, and brown-gray hair. Tongue smooth, atrophic and reddened. Thyroid gland moderately enlarged. No lymph node enlargement. Heart not enlarged. Blood pressure was 120 systolic and 80 diastolic. Lungs normal. Liver and spleen not palpable. Neurologic examination: Arm jerks equal and active; knee and ankle jerks not obtained; Babinski moderately positive response; absent ankle clonus; absent vibratory sense over the lower legs; Romberg test positive; gait moderately ataxic. The finger nails showed evidence of dystrophy.

Laboratory findings: (See Table 3 for red blood cells and hemoglobin.) White blood cells, 5200 per c.mm.; neutrophils, 52.5 per cent; lymphocytes, 37; monocytes, 7.5; eosinophils, 3. The red blood cells appeared on the average to be small and this was borne out by measurements. They were definitely achromic and varied markedly in size and shape. Blood platelets were present in normal numbers. Icteric index, 3. Fragility test: Hemolysis began at 0.48 and was complete in 0.16 per cent. Gastric analysis: No free hydrochloric acid 1 hour after histamin subcutaneously; peptic activity present but much diminished.

The patient improved slowly but very definitely upon the treatment indicated in Table 3. The mean corpuscular volume rose above normal during treatment, and a low color index was transformed to a high color index (Fig. 2). Paresthesias definitely diminished and she thought she could walk better, although to all appearances her ataxia was about the same.

The outstanding features of this case were the presence of combined system disease, achlorhydria, microcytic blood picture passing later to a macrocytic blood picture under the influence of iron. There was a reasonably satisfactory diet but one containing 8 cups of tea and a large amount of bread. There was abnormal fragility of the red blood cells, a history of easy bruising and koilonychia.

Fannie M., the tenth and last member of the second generation, was living and well in New York State. She was not known to be anemic. It was thought that there had been no trouble with her catamenia. She had 2 children who were perfectly well and not pale.

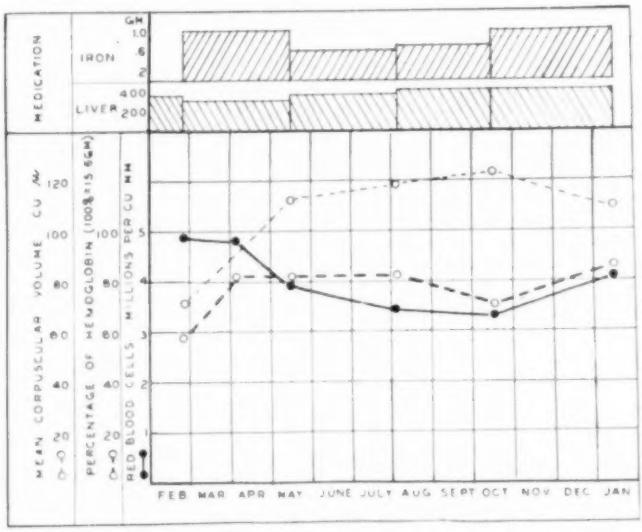

FIG. 2.—Changes in the blood of Gertrude M.

TABLE 3.—CASE OF GERTRUDE M.

Date.	R.b.c., millions per c.mm.	Hemoglobin, per cent.	Mean corpuscular volume, cu. micra.	Liver, and liver extract, No. 343. Grams daily.	Iron and ammonium citrate. Grams of iron daily.
Feb. 27*	4.93	57	71	250	1.0
April 3	4.81	81	...	250	1.0
May 16	3.81	81	112	400	0.6
Aug. 6	3.42	82	118	400	0.6
Oct. 17	3.25	69	123	400	1.0
Jan. 16	4.06	86	111		

* About 370 grams of liver were taken daily for 3 years before observation. No iron was taken.

Third Generation. Of this generation 5 have been examined and are reported here.

Hazel M. (second child of Elizabeth M.), aged 35 years, single, office worker, was seen briefly in May, 1931. She complained of a constant bloody vaginal discharge for 8 years. Menses began at 14 years, occurred monthly, lasted 6 days and were not profuse until 8 years previously, when she began to have a constant flow, usually somewhat bloody, requiring 1 pad a day, and a profuse flow of blood at the regular time of menstruation. Five years previously her uterus was curetted but without relief. Since

the onset of menorrhagia she had been troubled by dyspnea and palpitation, although she had not stopped work. One year previously, because her "metabolism test" was low, she began to take "6 thyroid tablets" a day. She thought these helped her strength, but she discontinued this therapy after several months. She never felt sensitive to cold or noticed loss of hair. She had gained 30 pounds in 3 or 4 years (present weight, 190 pounds). She stated that she bruised easily and that her finger nails broke easily. Her lips tended to crack easily. Her past history revealed nothing remarkable. Her hair turned gray when she was 25 years of age.

Physical examination revealed a rather obese woman with gray hair (not sparse) and light blue eyes. She was moderately pale. Her tongue was not atrophic; the tip was covered with large, smooth papillæ. There were several large white scars in the fundus of the right eye, and the disc was slightly blurred. The fundus of the left eye was normal. The thyroid gland was not enlarged. The heart, lungs and abdomen were negative. Blood pressure was 100 systolic and 60 diastolic. Spleen not palpable. The reflexes were normal. There were a few ecchymoses on the thighs. There was moderate dystrophy of the finger nails.

Laboratory examination: Red blood cells, 5,060,000 per c.mm.; hemoglobin, 63 per cent. The red cells were small and achromic with moderate variation in size and marked variation in shape. Mean corpuscular volume, 74 cu. micra (normal extremes, 85 to 95 cu. micra). Fragility tests: Hemolysis began in 0.5 and was not complete in 0.18 per cent. White blood cells, 10,400 per c.mm.; neutrophils, 57 per cent; lymphocytes, 33; monocytes, 7.5; eosinophils, 2; basophils, 0.5. Blood platelets definitely increased. Icteric index, 5. Gastric analysis showed maximal free hydrochloric acid of only 18, 1 hour after histamin subcutaneously. The peptic activity was somewhat reduced.

She was ordered to take 6 gm. of iron and ammonium citrate daily, but because of diarrhea was able to take only 2 to 4 gm. Three months later the red blood cells were 4,960,000 per c.mm.; mean corpuscular volume, 84 cu. micra; hemoglobin, 80 per cent. She felt improved in strength. The pronounced metrorrhagia had ceased, but the amount of menstrual flow was still increased. Eight months after the start of iron therapy she reported that she had had normal menses for several months, although she was troubled somewhat by leucorrhea. The red blood cells were 5,390,000; mean corpuscular volume, 89 cu. micra; hemoglobin, 96 per cent.

This case is interesting from the following standpoints: Menorrhagia, which was present also in the patient's mother and was relieved during the course of iron therapy, easy bruising, dystrophy of the nails and a microcytic blood picture which, in sharp contrast to the other cases, did not become macrocytic under iron treatment.

Gertrude M. (youngest daughter of Elizabeth M.) was seen, August 30, 1931. She was 28 years of age, single, clerk, who felt strong and well up to a year previously. During the past year she had a little recurrent pain in the right upper quadrant, with "bilious attacks." She thought that at these times her color became slightly yellow. She never noticed light-colored stools or dark urine. Eight years previously she had a swelling in the neck which was thought to be "goiter." She was treated by her doctor with biweekly internal throat applications of iodin for 6 months, after which the swelling subsided. Her diet had always been rich in fruit, vegetables and red meat. She never had a sore tongue, paresthesias or diarrhea. Her periods were scanty and came about every 5 weeks. Her finger nails seemed to be brittle. She never noticed easy bruising.

Physical examination revealed a girl of normal appearance, with brown hair and blue eyes. Tongue not atrophic. Thyroid gland palpable but

FIG. 3*a*

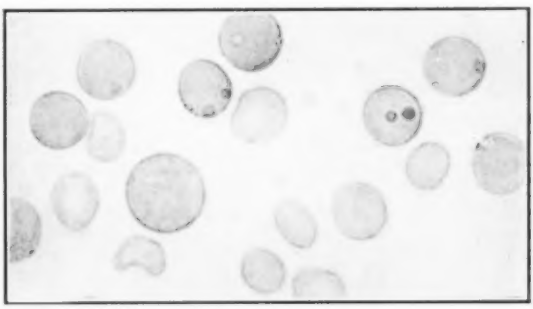

FIG. 3*b*

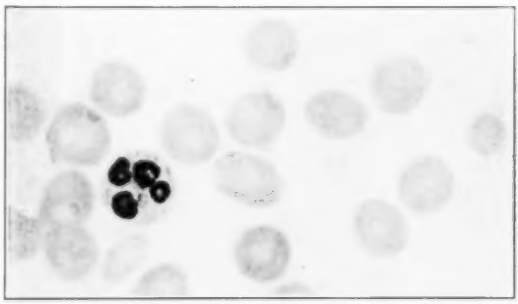

FIG. 3*c*

FIG. 3*a*, *b* and *c*.—Photomicrographs (× 1500) of blood smears on JessieIS., at different stages of treatment. Data given in Table 2; 3*a* = February, 27; 3*b* = May, 16; 3*c* = August, 27.

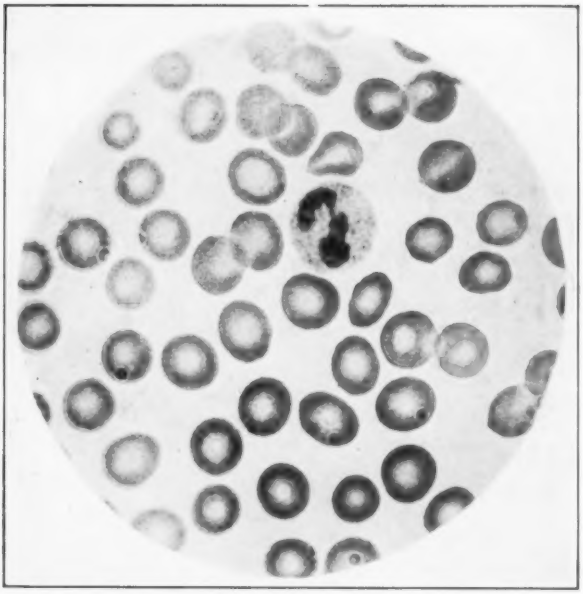

FIG. 4*a*.—Photomicrograph of blood smear on Allen S. (son of Jessie S.) (× 1500). Red blood cells, 4,310,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume, 106 cu. micra.

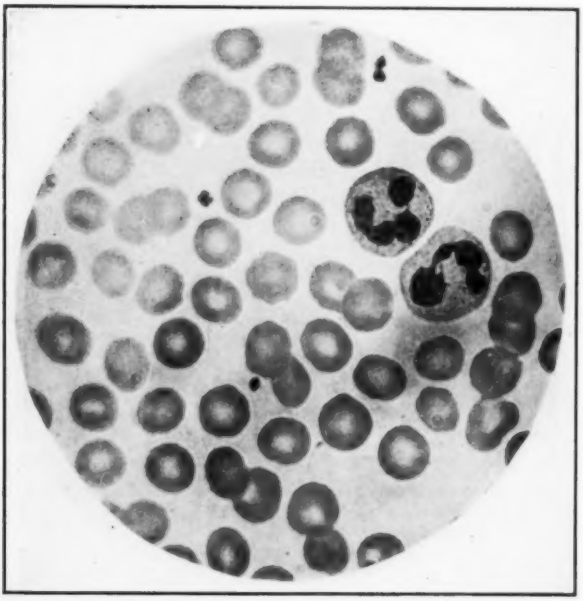

FIG. 4*b*.—Photomicrograph of blood smear on a normal man for comparison (× 1500). Red blood cells, 5,100,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume 81 cu. micra.

not enlarged. Reflexes normal. No definite evidence of dystrophy of the nails.

Blood examination: Red blood cells, 4,720,000 per c.mm.; hemoglobin, 82 per cent. The red cells appeared normal in size and showed very moderate variation in shape. They were not achromic. Mean corpuscular volume, 88 cu. micra. Fragility test: Hemolysis began at 0.46 and was complete at 0.3 per cent. White blood cells, 10,400 per c.mm.; neutrophils, 65 per cent; eosinophils, 0.5; basophils, 1.5; lymphocytes, 24; monocytes, 9. The blood platelets were normal.

Gastric analysis revealed a normal amount of free hydrochloric acid 20 minutes after histamin.

Of note in this case were the history of gastrointestinal and thyroid gland disturbance and the very slight changes in the red blood cells.

Malcolm S. (the second child of Jessie S.) was seen on September 17, 1931. He was 26 years of age, single, draftsman. He had always been in good health and had had no serious illnesses. For 3 years he had suffered from headaches, usually left-sided, sometimes accompanied by scotomata, often occurring on Sundays. He had had no sore tongue, diarrhea or paresthesias and no history suggesting anemia.

Physical examination showed a well-developed and nourished young man with dark brown and sparse hair and gray eyes. Skin showed a few lesions of psoriasis on the scalp and legs. Tongue not atrophic; thyroid gland not enlarged. Heart, lungs and abdomen negative. Reflexes normal.

Laboratory findings: Red blood cells, 4,450,000 per c.mm.; hemoglobin, 90 per cent. The red cells showed a very slight but definitely increased variation in size and shape. Mean corpuscular volume, 99 cu. micra. The fragility of the red corpuscles was within normal limits. Count of the white blood cells, 6000; neutrophils, 51.5 per cent; eosinophils, 0.5; basophils, 0.5; lymphocytes, 34; monocytes, 13.5. These examinations were repeated and the findings confirmed 3 months later. Free hydrochloric acid was present in the gastric contents in normal amount.

Important findings: Increased mean corpuscular volume and slight variation in size and shape of the red blood cells, in the presence of no obvious anemia and normal gastric analysis; mild migraine.

Allan S. (youngest son of Jessie S.), aged 23 years, single, hosiery factory worker, was seen on August 6, 1931. He was considered always to have been in perfect health. He never had a sore tongue or intestinal disturbances. His appetite was good and he had always eaten a generous diet of a wide variety of food. His tongue appeared normal. He had dark brown hair and blue eyes. His finger nails were normal. There was a fine tremor of the hands. The thyroid gland was moderately enlarged. The spleen was not palpable. Reflexes were normal and vibratory sense undiminished over the tibiæ.

Laboratory findings: Red blood cell, 4,310,000 per c.mm.; hemoglobin, 91 per cent. The red cells appeared somewhat large but only rarely was there seen either a large or rather small red blood cell (Fig. 4). Mean corpuscular volume, 102 cu. micra (normal extremes, 85 to 95 cu. micra). Fragility test: Hemolysis began at 0.46 and was complete at 0.26 per cent. White blood cells, 6800 per c.mm.; neutrophils, 47 per cent; eosinophils, 2; basophils, 2; lymphocytes, 40; monocytes, 9. Blood platelets present in normal numbers. A blood examination 3 weeks later showed red blood cells, 4,140,000; hemoglobin, 91 per cent; mean corpuscular volume, 106 cu. micra. Gastric analysis showed normal free hydrochloric acid.

Important findings: There was an increased mean corpuscular volume and slight changes in the red cells on examination of the blood film, but no definite anemia and normal gastric juice. The thyroid gland was enlarged.

Ruth M. (only child of Gertrude M.), aged 21 years, single, office worker. She felt strong and had been considered to be in perfect health with the exception of dysmenorrhea, which had not been incapacitating. She had had no menorrhagia and had no symptoms of anemia. Her diet had always been moderately reduced in vegetables and meat. Her paternal grandmother, residing in Detroit, was said to have pernicious anemia and difficulty in walking, and was improving under suitable therapy.

Physical examination showed a somewhat obese girl of a normal appearance with brown-black hair and gray eyes. Tongue not atrophic. Thyroid gland not enlarged. Heart, lungs and abdomen normal. Reflexes normal.

Laboratory findings: Red blood cells, 4,330,000 per c.mm.; hemoglobin, 84 per cent; the red blood cells appeared normal in size and shape. Mean corpuscular volume, 87 cu. micra. Fragility test: Hemolysis began at 0.46 and was complete at 0.28 per cent. White blood cells, 9700; neutrophils, 49.5 per cent; eosinophils, 2; basophils, 2; lymphocytes, 34.5; monocytes, 12. Blood platelets present in normal numbers. Gastric analysis showed free hydrochloric acid present in normal quantity.

This girl appeared to be in normal health but her family history was unusual.

Discussion. Table 1 summarizes the outstanding facts concerning this family. Attention is called to the presence of cholecystitis, migraine and an enlarged thyroid gland in several of the members; but it is not intended here to discuss their relationship to the familial anemia which may quite possibly exist. Neuburger[38] described a patient with pernicious anemia who had enlargement of the thyroid gland, and whose mother and daughter also had thyroid enlargement. Meulengracht,[39] on the basis of 8 cases, believed that there was a relationship between pernicious anemia and Basedow's disease.

From various points of view, one can plausibly consider that both pernicious anemia and idiopathic hypochromic anemia occurred in each of 3 sisters of the second generation, namely, Elizabeth M., Jessie S. and Gertrude M. Elizabeth M. and Jessie S., in 1916, and Jessie S. and Gertrude M., in 1931, had anemia with a low color index. Elizabeth M., in 1922, was demonstrated to have a high color index and, in 1931, combined system disease and, although then no definite anemia, a color index of a little over 1 and slight poikilocytosis—a picture compatible with pernicious anemia with combined system disease in partial remission. Jessie S. also had combined system disease in 1931, but at this time she had a severe hypochromic anemia. She had been taking liver extract. Under the administration of iron the red blood cells became megalocytic until the anemia was at length abolished by liver and iron therapy, and then the red blood cells became normocytic. Gertrude M. showed, when first seen, a hypochromic anemia with advanced combined system disease. She also had been taking liver extract. This was continued, but under the administration of iron her blood went through changes similar to those of Jessie S. Both sisters had great symptomatic improvement. Tables 2 and 3 and Figs. 1, 2

and 3 illustrate these changes. It is interesting that the red blood cell count fell in both cases when iron was first given. The explanation for this lies in the fact that the newly formed red blood cells had a much larger content of hemoglobin than formerly. (Fig. 3, *b*, which shows several macrocytes well filled with hemoglobin.) Other patients with idiopathic hypochromic anemia with achlorhydria but without evidence of a pernicious anemia element, when given iron, have not developed macrocytosis. In pure idiopathic hypochromic anemia there is presumably no lack of stroma-building substance.

Each of these 3 sisters had achlorhydria. It is noteworthy that in their cases the combined system disease had been very slowly progressive, which is apparently true also of their brother, James M. The anemia appears also to have been on the whole very slowly progressive. Menorrhagia occurs in about 20 per cent of cases of idiopathic hypochromic anemia with achlorhydria and may intensify the anemia. Easy bruising and dystrophy of the nails are also common in severe idiopathic hypochromic anemia. An enlarged spleen is found occasionally in both types of anemia and a history of an undesirable diet occurs frequently in both types. It is probably both a result of and a contributing factor to the anemia.

The fragility tests of the red blood corpuscles in these sisters showed a slightly decreased minimal and a pronounced increased maximal resistance, that is to say, an increased resistance span. Such an increased span has been described by Hill[40] in pernicious and hypochromic anemia, by Waugh[41] in hypochromic anemia, by Minot and Buckman[42] in erythremia and has been studied by Minot[21] in various conditions. It is not characteristic of familial hemolytic jaundice which shows a decreased minimal and maximal resistance. Moreover, the return of the fragility of the red blood cells to normal limits, as the anemia improved under liver and iron therapy, is also not characteristic of familial hemolytic jaundice.

The case of Hazel M., daughter of Elizabeth M., is characteristic of idiopathic hypochromic anemia, with reduced free hydrochloric acid in the gastric contents. She was completely alleviated by iron therapy alone. In her case there is, as yet, no evidence of pernicious anemia.

The presence of a hypochromic blood picture in the female members of the family, and its absence in the male members, is a fact worthy of emphasis. That this is not coincidence is shown by the fact that in other similar families recorded in the literature the hypochromic anemia occurs particularly in females and is rare in males. These facts, together with the occurrence of chlorosis in girls and rarely in boys, still await explanation.

The presence of a megalocytic blood picture in the 2 sons of Jessie S. (Fig. 4 and Table 1), without anemia and without reduction in gastric free hydrochloric acid, is at first sight exceedingly perplex-

ing. However, Castle and his coworkers[1] have definitely proven that absence of free hydrochloric acid is not a *sine qua non* of pernicious anemia. Moreover, appreciable amounts of the gastric specific factor have been found in a few cases of pernicious anemia, having free hydrochloric acid present in the gastric contents.[1,42] It is very probable that in these 2 young men there is some reduction in the specific factor of the stomach secretion, and that one is witnessing here an extremely early form of pernicious anemia in younger members of a family in which the disease has a very slowly progressive character. Such a megalocytosis without definite anemia has been reported in members of pernicious anemia families by Todd[16] and others. Allan M., the uncle of the 2 boys, may be considered to have a further advanced stage of the disease with nearly complete absence of free hydrochloric acid and probably a greater reduction in the gastric specific factor. His disease has taken a form in which a lower bowel disturbance is predominant, as is not unusual early in pernicious anemia.

It is believed that in this family there is an inherited tendency to reduce gastric function, which is responsible for the different types of anemia. There is much proof of a direct causal relationship between diminished gastric secretion and pernicious anemia. In general, the increasing evidence of the relationship of disturbances of the gastrointestinal tract to anemia[44] leads to suspect such a relationship in idiopathic hypochromic anemia.[3] The presence of hypochromic anemia in members of a family and, moreover, its presence in individual members who also have pernicious anemia are indicative of a similar causal relationship. This also helps to clarify the belief that idiopathic hypochromic anemia is primarily the result of a deficiency, conditioned by a disorder of the gastrointestinal tract which leads to an inability to absorb or utilize hemoglobin-building material from the food.

Summary and Conclusions. 1. The literature reveals abundant evidence to prove an interrelationship between pernicious anemia and idiopathic hypochromic anemia, and their common relation to disorders of the gastrointestinal tract, exemplified by achlorhydria.

2. A family is reported in which pernicious anemia and idiopathic hypochromic anemia with achlorhydria were both present in each of 3 sisters. The histories and blood findings of other members of the family were suggestive of borderline anemic states, while several had either pernicious anemia or hypochromic anemia.

3. By analogy with the well-corroborated hypothesis of Castle, that pernicious anemia is secondary to the absence of a specific factor in the stomach, it is believed that idiopathic hypochromic anemia is primarily the result of a deficiency, conditioned by a disorder of the gastrointestinal tract, leading to an inability to absorb or utilize hemoglobin-building material from the food.

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ERYTHROCYTES IN PELLAGRA.

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A reinvestigation of the erythrocytes of pellagrins, using the most accurate methods now available, seemed to be indicated on account of the existence of many similarities between pellagra and

pernicious anemia. Our results are reported, although they confirm previous work done with less accurate methods. The extensive literature on the blood picture of pellagra has been thoroughly reviewed by Huck,[1] who also made studies of 20 patients. He found that other observers reported that in uncomplicated pellagra there may be no anemia or it may be present in a mild, moderate or severe degree and be of the chlorotic or secondary type. All of Huck's patients showed secondary anemia. Mollow and Klein,[2] in Bulgaria, in an extensive study of the blood cells of pellagrins, found the anemia always of the secondary type except for 1 patient who, after suffering from recurrent pellagra for many years, finally showed the blood picture, as well as the clinical features, of pernicious anemia.

Methods and Standards of Accuracy. Venous blood was drawn into a clean, dry syringe, using as little stasis as possible, and placed in a 15 by 150 mm. test tube. It was defibrinated with a small dry glass rod and kept stoppered to prevent evaporation. All samples were taken after a 12-hour abstinence from food; intake of fluids was not limited. The hemocytometer and diluting pipettes used were certified by the United States Bureau of Standards. The erythrocyte count reported was the average of two or more, usually three, estimations which agreed within 200,000 cells. Each estimation involved the use of a clean, dry diluting pipette and a clean, dry hemocytometer. Parallel erythrocyte counts were made on a series of bloods, using both oxalated and defibrinated specimens of the same blood and no appreciable differences were noted. The hematocrit tube, 100 mm. deep, described by Wintrobe[3] and used in his later studies, was used throughout. Of course, no correction for shrinkage was necessary since no anticoagulant was used. The Newcomer method for hemoglobin was employed, the glass disk carefully standardized by Dr. Wintrobe being used.

The group of 50 pellagrins whom we have studied was made up of 39 colored women, 7 white women and 4 white men. In none of them was the diagnosis doubtful. The age of our pellagrins by decades was as follows: (1) 1; (2) 4, 1 below the age of puberty; (3) 16; (4) 17; (5) 7; (6) 5.

In the main, the patients were studied without selection as they were admitted to the hospital. However, for a few weeks admissions were so frequent that not all could be studied and choice was made of those who had skin lesions of shortest duration. Some were omitted because of complications, such as stricture of the rectum, although a few of these cases were included. Eighty per cent showed or gave history of glossitis; 50 per cent exhibited serious mental symptoms during their stay in the hospital. Of the 31 whose gastric analyses were done 10 showed the presence of hydrochloric acid and 21 showed its absence. Twenty-nine of the 50 patients left the hospital as improved, 6 as unimproved and 15 (30 per cent) died while in the hospital. Six patients told of previous attacks of pellagra, while the others were apparently in the first attack. It is of some interest that only 1 of the 6 cases with a history of previous attacks showed definite anemia. There were 29 patients (58 per cent) who had shown skin lesions for 1 month or less and 12 (24 per cent) for 2 weeks or less; 3 developed the dermatitis while in the ward. Since these patients are hospital bed patients, they surely represent in the main examples of severe pellagra. This is supported by the high death rate.

Using the same technique and procedure, 21 healthy young men (medical students) were studied.

The standards for normal are given in the first lines in Table 1. These

values are in the main from Wintrobe's review.[4] In some instances the range of normal values has been extended to include results of our study of healthy men. It will be noted that the average hemoglobin value for normals for both men and women is 15.5 gm. (104 per cent), while the average for young men is 16.2 gm. (112 per cent). It seems rather extraordinary that the average hemoglobin value for normal individuals should have a value of greater than 100 per cent. This is due to the fact that the value represented by 100 per cent hemoglobin, 14.5 gm., is based on the average hemoglobin content of healthy individuals calculated to a red cell count of 5,000,000. Since the average normal red cell count is greater than 5,000,000, the average hemoglobin content is greater than the accepted standard for 100 per cent. This confusing maneuver is necessary in order to preserve the traditional color index which demands that 100 per cent represent the hemoglobin content of a normal blood which has a cell count of 5,000,000, which is less than the normal average count. The necessity for such an artificial standard in order to maintain the usefulness of the color index emphasizes the need for more rational factors which will express characteristics of erythrocytes in absolute values. Probably the most useful characteristic of red cells which may be expressed by a figure is the average size, preferably stated as volume. The method of calculation of the average volume of erythrocytes in cubic micra from known red cell count and hematocrit readings was introduced by Haden,[5] who pointed out the value of such calculations in the study of anemia. However, Haden[6] prefers to express average corpuscular volume in terms of per cent of normal, *i. e.*, by the volume index of Capps.[7] Wintrobe[8] has advocated the custom of expressing the characteristics of erythrocytes in absolute values rather than relative to normal. Since the size of the normal red blood cell is a range rather than an exact level and on account of considerations mentioned above, Wintrobe's position seems quite sound. The two other useful characteristics of red blood cells which may be expressed in absolute rather than relative units are, according to Wintrobe's terminology:[8] mean corpuscular hemoglobin and corpuscular hemoglobin concentration.

In the cursory statistical analysis of our data we have used the results of only the first study of each patient in order to avoid distortion due to the repeated studies made on a few patients with marked anemia. One exception to this rule will be noted in Fig. 3, where 69 observations were used. As to the degree of anemia, the 50 pellagrins were grouped as follows: Without anemia, *i. e.*, with more than 12 gm. of hemoglobin per 100 cc., there were 28 patients (56 per cent); with slight or questionable anemia, 10 to 12 gm. hemoglobin per 100 cc., 8 patients (16 per cent); with moderate anemia, 8 to 10 gm. of hemoglobin, 6 patients (12 per cent) and extremely severe anemia, less than 6 gm. of hemoglobin, 2 patients (4 per cent). Of the 15 patients who died 10 showed no anemia, while 3 showed severe and 2 moderate anemia.

By inspection of the histograms of Fig. 1 and the graph in Fig. 2 it will be noted that the size of erythrocytes of our pellagrins was with one exception either within the normal range or smaller than normal. In only 1 instance did mean corpuscular volume exceed 100 cubic micra and that was only 103 cubic micra. The erythrocytes showing the classic picture of pernicious anemia have

TABLE 1.—DATA FOR 50 CASES OF TYPICAL PELLAGRA AND 1 CASE OF SPRUE RESEMBLING PELLAGRA.

Case.	Age.	Sex.	Color.	Interval since previous study.	Recent diarrhea.	Duration of dermatitis.	Glossitis.	Psychosis.	Free HCl, stomach.	Condition at discharge.	R.b.c., millions.	Per cent r.b.c. hematocrit.	Hemoglobin, gm. per 100 cc.	Hemoglobin per cent.	Corpuscular volume, cu. micra.	Mean corpuscular hemoglobin ?? (10^{-12} gm.).	Corpuscular hemoglobin concentration per cent.	Volume index.	Color index.	Saturation index.	Remarks.
											7.30	56.0	20.0	130	100	31.5	39.0	1.20	1.20	1.25	Maximum } Values
											5.50	43.0	16.2	112	83	28.5	35.0	0.95	0.97	1.02	Mean } for
											4.40	34.0	11.5	79	70	26.5	33.0	0.73	0.80	0.80	Minimum } normal.
1	33	F	C		+	4 D	+	0	0	I	2.87	14.9	5.59	39	52	19.5	37.5	0.61	0.68	1.11	Luetic proctitis.
				10 D	..	..	..	..	..	..	2.36	10.7	3.92	27	45	16.6	36.7	0.55	0.58	1.05	
2	37	F	C	..	0	2 M	+	0	0	I	1.92	10.8	3.74	26	55	19.5	34.7	0.68	0.66	0.97	Luetic ulcers of leg.
				4 D	..	..	..	..	..	..	1.88	11.9	4.40	30	63	23.4	37.0	0.74	0.81	1.09	
3	33	F	W	..	..	3 Y / 6 M	..	+	..	U	4.11	23.1	7.30	51	56	17.8	31.6	0.67	0.63	0.94	Second attack.
4	37	F	C	..	0	1 W	+	0	+	I	4.11	24.8	8.05	56	60	19.6	32.5	0.73	0.68	0.94	Ovarian cyst; salpingitis.
				21 D	..	..	..	..	..	..	3.55	22.7	7.84	55	64	22.1	34.5	0.76	0.77	1.01	
5	21	F	C	..	0	6 M	..	..	0	I	5.47	33.3	10.96	76	61	24.6	32.9	0.73	0.70	0.96	Congenital syphilis.
6	31	F	C	..	0	2 D	+	0	0	I	6.06	38.3	13.30	93	63	22.0	34.7	0.76	0.77	1.01	
				3 D	..	..	..	..	..	..	5.51	33.5	12.66	88	61	23.0	37.8	0.72	0.80	1.11	
7	28	F	C	..	0	3 M	..	+	..	D	6.54	41.7	14.74	102	64	22.6	35.4	0.77	0.79	1.03	
				7 D	..	..	..	..	..	..	4.35	35.2	14.10	98	80	32.4	32.4	0.97	1.14	1.18	
8	24	F	C	..	0	3 W	+	+	..	D	3.85	24.9	7.84	55	65	19.8	31.5	0.78	0.71	0.91	Tuberculous peritonitis.
9	28	F	C	..	0	4 M	+	0	..	I	4.73	31.3	8.90	62	66	18.8	28.4	0.78	0.66	0.85	
10	35	F	C	..	+	4 M	+	+	+	U	3.93	25.9	7.84	55	66	19.9	30.2	0.80	0.70	0.87	Luetic proctitis with stricture terminal.
11	50	F	C	..	..	3 M	..	+	..	D	5.76	38.6	13.50	94	67	23.4	35.0	0.81	0.82	0.99	
12	28	F	W	..	+	2 W	+	0	0	I	6.51	44.5	15.75	109	68	24.2	35.4	0.83	0.84	1.01	
13	35	M	W	..	+	5 W	+	+	..	I	5.99	39.9	13.30	93	69	22.2	33.4	0.80	0.77	0.96	Imbecile.
14	36	F	C	..	..	3 D	+	0	..	I	4.79	32.8	12.46	87	69	26.0	38.0	0.82	0.91	1.11	Partial obstruction of cecum.
15	36	F	C	..	0	3 W	0	0	+	D	3.49	24.3	7.60	53	70	21.8	31.3	0.83	0.76	0.92	Stricture of cecum.
				10 D	..	..	..	..	..	..	3.50	23.0	9.10	63	66	26.0	39.6	0.79	0.90	1.14	
				22 D	..	..	..	..	..	..	3.04	23.3	7.84	55	77	25.8	33.6	0.93	0.90	0.97	
16	32	F	W	..	+	15 Y / 6 W	+	+	..	D	5.57	36.9	14.53	101	71	26.1	39.4	0.80	0.91	1.14	
17	24	F	C	..	0	3 W	..	..	+	I	6.05	42.7	14.53	101	71	24.0	34.1	0.83	0.84	1.01	
18	40	F	C	..	0	2 W	0	0	+	I	4.79	33.8	11.80	82	71	24.6	34.9	0.84	0.86	1.02	
				7 D	..	..	..	..	..	..	5.08	35.5	13.30	93	70	26.2	37.5	0.83	0.91	1.10	
19	29	F	C	..	..	2 W	+	..	..	D	5.04	36.1	12.00	84	72	23.8	38.6	0.87	0.83	0.96	Vomiting; postoperative adhesions.

20	40	F	C		+	2 M	4	0	0	I	4.68	34.7	11.38	79	72	24.3	32.8	0.88	0.84	0.96		
				1 D	..	..	..	..	..	..	4.69	33.4	11.38	79	71	24.2	34.1	0.85	0.84	0.99		
				16 D	..	..	..	..	..	..	4.86	40.2	13.50	94	83	27.8	33.7	0.99	0.97	0.98		
21	51	M	W	..	+	5 W	+	0	..	U	7.24	52.5	18.68	130	72	25.8	35.8	0.87	0.90	1.03		
22	50	F	C	..	0	3 W	0	0	..	U	5.06	36.4	11.38	79	72	15.0	31.2	0.81	0.78	0.91		
23	40	M	W	..	+	3 W	+	0	0	I	7.42	53.6	21.10	153	72	28.5	39.3	0.87	1.03	1.18		
24	27	F	C	..	+	1 M	+	0	0	I	4.87	35.0	12.25	85	72	25.2	35.0	0.87	0.88	1.01		
25	45	F	C	..	+	3 W	..	..	..	D	3.77	27.5	9.50	66	73	25.2	34.5	0.88	0.88	1.00		
26	36	F	C	..	+	1 M	..	0	+	I	4.96	36.1	12.66	88	73	25.5	35.1	0.88	0.89	1.01		
27	41	F	C	..	+	1 M	+	+	0	D	3.06	22.5	7.40	51	74	24.2	32.9	0.89	0.84	0.94		
28	40	F	C	..	0	3 W	..	0	0	I	4.69	34.6	12.00	84	74	25.6	34.7	0.89	0.89	1.00		
29	17	F	C	..	+	4 W	+	0	0	I	4.18	31.0	11.38	79	74	18.6	36.7	0.89	0.95	1.07		
30	36	F	C	..	+	3 W	0	0	0	I	3.43	25.8	8.48	59	75	24.7	32.9	0.90	0.86	0.96		
				11 D	..	..	..	..	..	..	3.07	23.6	8.48	59	77	27.6	35.9	0.93	0.97	1.04		
				17 D	..	..	..	..	..	..	5.35	34.3	..	..	73	..	..	0.77				
31	50	F	C	..	+	3 M	..	+	..	D	3.85	29.1	9.10	63	76	23.6	31.3	0.90	0.82	0.91	Mossy foot.	
32	21	F	C	..	+	2 W	..	..	..	I	4.68	35.7	11.59	80	76	24.7	32.7	0.92	0.86	0.94		
33	23	F	C	..	+	1 W	..	+	+	I	4.53	34.5	11.38	79	76	25.1	33.0	0.91	0.87	0.96		
34	32	F	W	..	+	2 Y / 6 W	+	+	0	D	4.72	35.8	12.00	84	76	25.5	33.7	0.91	0.89	0.98		
35	24	F	C	..	..	1 M	..	..	..	I	3.91	30.2	10.77	75	76	27.4	35.5	0.94	0.96	1.03		
36	28	F	C	..	+	2 W	+	0	0	I	3.50	28.1	9.10	63	80	26.0	31.9	0.99	0.90	0.99		
				6 D	..	..	..	..	..	..	3.64	24.3	9.30	65	67	25.6	38.3	0.80	0.89	1.11		
				13 D	..	..	..	..	..	..	2.43	15.5	6.65	46	64	27.4	42.8	0.76	0.95	1.25		
				17 D	..	..	..	..	..	..	2.88	22.6	7.84	55	78	27.2	34.7	0.93	0.95	1.02		
37	33	F	C	..	0	8 Y / 3 M	+	0	..	I	5.22	41.9	15.32	107	80	29.4	36.6	0.96	1.03	1.07		
38	28	F	W	..	+	3 Y / 6 W	+	+	0	I	4.95	40.0	15.12	105	81	30.6	37.8	0.97	1.06	1.09		
39	35	F	C	..	+	1 M	0	0	0	U	2.42	19.5	7.26	51	81	30.0	37.2	0.97	1.05	1.08		
				6 D	..	..	..	..	..	..	2.87	23.1	8.70	61	82	30.3	37.7	0.96	1.06	1.10		
40	25	F	W	..	0	5 Y / 6 W	0	0	+	I	5.04	41.7	15.55	108	82	30.9	37.3	1.00	1.08	1.08		
41	16	F	C	..	+	2 M	+	0	0	D	6.23	51.5	16.60	115	83	26.7	32.3	0.97	0.93	0.96		
				1 D	..	..	..	..	..	..	4.85	41.2	15.12	105	83	31.2	36.8	1.02	1.08	1.04		
42	53	F	C	..	0	3 M	+	..	0	D	4.93	40.9	13.50	94	83	27.4	33.0	1.00	0.95	0.95		
				2 D	..	..	..	..	..	..	5.44	42.9	14.94	104	79	27.5	34.8	0.93	0.96	1.03		
43	31	F	C	..	+	1 M	..	+	0	D	5.98	50.3	17.65	123	84	29.5	35.0	1.10	1.12	1.02		
44	22	F	W	..	+	2 W	+	+	..	D	5.70	47.7	16.19	112	84	28.4	33.9	1.00	0.99	0.99		
45	7	F	C	..	+	3 W	0	0	+	I	5.24	44.6	13.10	91	85	25.0	29.4	1.02	0.87	0.85		
46	27	F	C	..	..	3 M	..	+	..	U	4.71	41.6	14.74	102	88	31.3	35.5	1.06	1.08	1.02		
47	19	F	C	..	0	3 W	..	+	0	I	4.11	36.5	13.70	95	89	33.4	37.5	1.07	1.16	1.09		
				9 D	..	..	..	..	..	..	5.28	39.8	13.50	94	76	25.5	33.9	0.91	0.89	0.98		
48	11	F	C	..	+	1 W	+	0	0	I	3.78	37.5	12.25	85	100	32.4	32.7	1.19	1.13	0.95		
49	42	F	C	..	0	4 W	+	+	0	D	4.81	48.1	16.60	115	100	34.0	33.9	1.20	1.20	1.00		
				13 D	..	..	..	..	..	I	5.77	46.6	16.82	117	81	29.2	36.1	0.97	1.02	1.05		
50	32	M	W	..	+	9 W	+	0	..	I	3.93	40.6	14.10	98	103	35.9	34.9	1.27	1.25	0.98		
51	32	M	W	..	+	6 W	+	0	+	I	3.03	34.6	12.88	90	114	42.5	37.3	1.36	1.48	1.09	Case of sprue.	

Cases arranged in order of ascending corpuscular volume. Patient's numbers correspond to those of graph. Age is expressed in years. Sex: F = female; M = male. Recent diarrhea: + = present during the 2 weeks before study; 0 = absent during same period. "Skin duration" refers to duration of dermatitis at time of study. D = days, W = weeks, M = months, Y = years. For cases with recurrent attacks, time since first attack and duration of present lesions are given. Psychosis: + = serious mental symptoms observed during stay in hospital. F HCl: + = presence of free hydrochloric acid in gastric contents after Ewald test meal. Condition at discharge: I = improved; U = unimproved; D = dead.

a mean corpuscular volume of from 110 to 150 cubic micra. Anemia when present was definitely of the normocytic or microcytic type and not of the macrocytic type.

As to how richly the erythrocytes are supplied with hemoglobin, the histogram in Fig. 1 shows that 34 per cent of the patients had a corpuscular hemoglobin concentration below the normal range, while 66 per cent were within the normal range. Haden[5] and Wintrobe[9] found subnormal concentration of corpuscular hemoglobin characteristic of secondary anemias due to chronic loss of blood. Only 7 of the 17 patients showing this type of cells showed

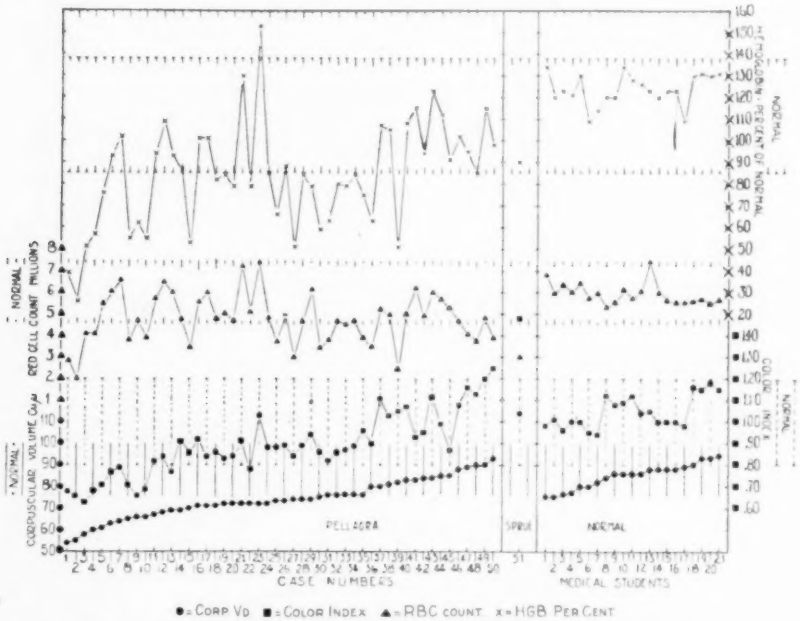
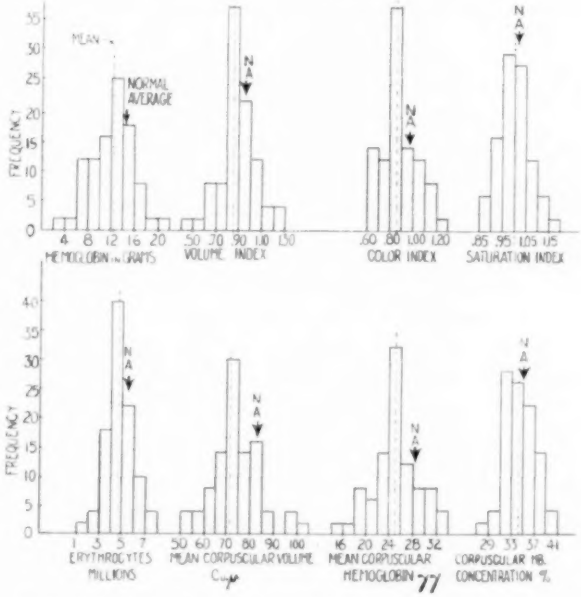


FIG. 1.—Data recorded are for first study on each of 50 typical pellagrins; 1 patient with sprue resembled pellagra clinically; and 21 healthy medical students. Same routine and technique used for all. One hundred per cent hemoglobin = 14.5 gm. per 100 cc.

clinical evidences of chronic blood loss. Among the 33 patients with normal concentration of hemoglobin in the red cells were 2 with extremely severe anemia and 7 others with slight anemia. All but 3 of the 17 patients with low corpuscular hemoglobin concentration had anemia of varying grade as indicated by hemoglobin content in grams per 100 cc. of blood. Therefore of the 24 patients with anemia of varying degree, 10 had erythrocytes with the normal concentration of hemoglobin, while 14 had cells containing less hemoglobin than their size demanded.

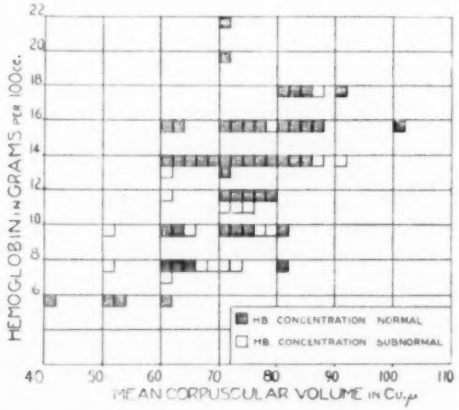
Examination of Fig. 3 will show that there was a relationship

FIG. 2.—FREQUENCY DISTRIBUTION OF VARIATION OF VARIOUS VALUES FOR 50 BLOODS FROM 50 PELLAGRINS.



Dotted lines show the means. NA = the normal average.

FIG. 3.—CORRELATION BETWEEN HEMOGLOBIN CONTENT OF BLOOD AND AVERAGE VOLUME OF THE RED CELLS (BASED ON 69 SPECIMENS OF BLOOD FROM 50 PATIENTS WITH PELLAGRA).



The distribution of bloods containing cells with subnormal concentration of hemoglobin is also shown. Each square represents one specimen of blood. Correlation coefficient = $+0.526 \pm 0.0059$.

between degree of anemia as measured by the hemoglobin content of the blood and size of the cells; patients with normal hemoglobin values usually had red cells of normal average volume, while those whose hemoglobin was less than normal usually had cells also smaller than normal, and roughly proportional to the hemoglobin level, expressed in grams per 100 cc., the correlation coefficient being $+0.526 \pm 0.0059$. This is in striking contrast with the blood of pernicious anemia. In this disease, as is well known, when anemia becomes more severe and hemoglobin content of the blood falls, the average volume of the red cells increases to far above the normal value.*

For a number of pellagrins the cells were smaller than normal though the red cell counts were not low. Fig. 3 shows the distribution of bloods made up of pale cells, that is, with less than the normal concentration of hemoglobin. Such cells were noted about as frequently in those with moderate anemia as in severe anemia.

Case 51 illustrates the possible value of the erythrocytic picture in the diagnosis of pellagra. This patient did not speak English and a satisfactory history was not obtained until several days after admission. He had a severe diarrhea and a sore tongue; his hands and feet showed desquamation of the skin with slight pigmentation. The affected areas did not show sharply defined borders, however. His erythrocytes were of the macrocytic type. In the differential diagnosis on admission pellagra occupied a prominent position. He later gave the history that his hands and feet had been edematous 1 month before and he was obviously suffering from arteriosclerotic heart disease with congestive failure which was no doubt aggravated by the anemia. The previously existing edema was thought to explain the skin lesions. His stools were frothy and bulky, and his gastric contents contained free hydrochloric acid. He was free of abnormal mental symptoms. His condition was called sprue rather than pellagra. The response to liver therapy tended to confirm that diagnosis.

A number of influences have been considered as possibly having a bearing upon the degree and type of anemia present in pellagra. It is interesting to note that of the 8 patients who showed a severe or extremely severe anemia 5 had other diseases, such as syphilis or organic intestinal disease, which might have played an important part in the production of anemia. One patient (Case 36), not included in the above 8, suffered from uncomplicated pellagra. She had 9.1 gm. of hemoglobin per 100 cc. of blood on admission, and 3 weeks later 6.65 gm. During this time there was considerable loss of blood from extensive ulcerated, but not obviously infected,

* A personal communication from Dr. M. M. Wintrobe, to whom I am greatly indebted, is as follows: "The coefficient of correlation between hemoglobin in grams and mean corpuscular volume for 657 determinations in pernicious anemia is -0.4960 ± 0.0294."

skin lesions. During the interval considerable dehydration had probably been overcome, which may have played an important part in the change in hemoglobin concentration of the blood. Intestinal parasites have not appeared to play an important part in the production of anemia in the group studied. It has been suggested by several observers that anemia of pellagra is dependent upon the presence of diarrhea, upon the loss of iron and other blood-building constituents by the bowel. The average hemoglobin content of the blood of 17 patients who had not suffered from diarrhea differed by less than 1 per cent from the average for 25 who had been suffering from diarrhea. Two patients with diarrhea whose hemoglobin percentages were very high, due apparently to dehydration, were excluded from these calculations. Concentration of the blood due to loss of body fluids may have been a factor in obscuring anemia in others of these patients. Determinations of circulating blood volume[10] carried out since the observations reported here were made have shown that the total quantity of erythrocytes in pellagra may frequently show more striking diminution than is indicated by hemoglobin or hematocrit readings. This is due to diminished plasma volume. It is probable that a greater absolute anemia existed, particularly in some of our patients who died, than the hemoglobin values indicated. The tendency toward high red cell counts and hemoglobin content noted in some of the normal young men in our series may also have been due to mild dehydration, since the specimens were taken early in the morning and before they had eaten breakfast.

Many of our patients gave most unsatisfactory histories concerning their diet. Among those thought to be reliable a number had taken regularly a diet containing fresh lean meat. Others, and the majority, had eaten little or no lean meat. Many had taken an abundance of fresh green vegetables. No difference in the degree or type of anemia could be detected in those whose diet was obviously faulty and those who had taken a fairly satisfactory diet. Also, there were no obvious differences in the blood pictures of those with achylia and those whose gastric contents contained free hydrochloric acid.

Many physicians have noticed and recorded the striking similarities existing between pernicious anemia and pellagra, especially of symptomatology and morbid anatomy. The proof within recent years of the beneficial effects of diet in pernicious anemia has suggested possible parallelism also in the matter of pathogenesis, particularly since foods which are hematopoietic in pernicious anemia are highly recommended for the pellagrin. The most characteristic single easily demonstrable abnormality of the patient with pernicious anemia is the macrocytic anemia. The contrasting tendency for anemia in pellagra to be normocytic or microcytic would seem to indicate a definite and significant difference in

pathogenesis in the two diseases, however much they may have in common.

Bliss[11] has suggested that iron deficiency might be the cause of pellagra. The demonstration that many pellagrins, particularly during the early stages of the disease, do not show anemia, does not support his hypothesis.

Summary. 1. Using the most accurate available methods, erythrocyte counts and determinations of hemoglobin and percentages of packed red cells have been made for 70 bloods from 50 patients with typical pellagra. The results with the calculated mean corpuscular volume, mean corpuscular hemoglobin, corpuscular hemoglobin concentration, volume index, color index and saturation index along with certain clinical features are reported in Table 1. The data for 1 case of sprue which might have been considered pellagra are included in the table.

2. In a graph the blood pictures of the 50 pellagrins are contrasted with those of 21 medical students and that of a case of sprue. In other graphs results are further analyzed.

3. Of the pellagrins 56 per cent showed no appreciable anemia; 16 per cent slight or questionable anemia; 12 per cent showed moderate anemia and 12 per cent a severe anemia, while 4 per cent showed an extremely severe anemia.

4. Two-thirds of the patients who died showed no anemia according to the methods and standards used.

5. Among those with severe anemia, other diseases which might have caused anemia were common.

6. Patients who suffered from diarrhea did not appear to be more anemic than those without diarrhea.

7. The influence of dehydration in obscuring anemia is discussed.

8. Anemia, when present, was definitely of the chlorotic, normocytic, or microcytic type, and in no instance of the macrocytic type.

9. Of the pellagrins 34 per cent had erythrocytes with corpuscular hemoglobin concentration less than normal, while for 66 per cent the concentration was within the normal range.

10. The average size of the red cells tended to diminish in proportion to the severity of the anemia, contrasting with the opposite rule for pernicious anemia.

11. The importance of the blood picture in the differential diagnosis between pellagra and pernicious anemia or sprue is emphasized.

NOTE.—We wish to record our gratitude to the late Dr. J. Birney Guthrie, through whose kindness and interest we had the privilege of studying the colored women pellagrins in this series. Throughout the study his keen enthusiasm for the investigation of pellagra was felt.

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THE NONFILAMENT POLYMORPHONUCLEAR NEUTROPHIL COUNT IN TYPHOID AND UNDULANT FEVER.

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Since the classification of the polymorphonuclear neutrophilic leukocytes by Arneth,[1] in 1904, there has been a gradual increase in our knowledge regarding their function. The development of the Schilling[10] index furnished a larger number of investigators with a more simple means of enumerating the various forms of polymorphonuclear neutrophils, and subsequent studies by Pons and Krumbhaar,[9] Cooke and Ponder,[2] Piney,[8] Farley, St. Clair and Reisinger,[3] and others have provided even the most inexperienced worker with efficient and practical methods.

The method suggested by Farley *et al.* is based on a simplification of the Cooke and Ponder classification of the polymorphonuclear neutrophils and is especially designed for routine clinical use. In this method the polymorphonuclear neutrophils are divided into two groups, the first being identical with Cooke and Ponder's Class I and the other group including their other four classes. The groups are designated by Farley as "nonfilament polymorphonuclears" and "filament polymorphonuclears," respectively. The nonfilament group includes those young or immature cells whose nuclear material is connected by broad bands; the filament group comprises older cells whose segments of nuclear material are joined by fine filaments. On the basis of 100 presumably normal adults, Farley *et al.* suggest 16 per cent nonfilament cells as the upper limit of

normal, and 8 per cent as the average. Medlar[6] regards as abnormal a nonfilament count higher than 8 per cent.

The value of such studies is becoming widely recognized. Arneth[1] and Cooke and Ponder[2] and many others have reported the increase of immature forms in acute infections; Goodale and Manning[5] have emphasized the supplementary value of the Schilling index in the diagnosis of acute appendicitis; Mullin and Large[7] found that the nonfilament count follows the course of the infection more closely than does the total leukocyte count; Farley *et al.*[3] and Weiss[11,12] have emphasized the value of the method in determining the degree of bone marrow response to infection and shown that the actual degree of bone marrow response may be reflected in the number of immature cells but not in the total leukocyte count.

The present report is concerned with the nonfilament neutrophil count in two diseases which are usually associated with leukopenia. The majority of the counts were made on the day of admission of the patient to the hospital. The day of the disease is, of course, only an estimation. Since leukopenia is regarded as associated with either an inhibition of the bone marrow by bacterial or other toxins, or with an increased destruction of the leukocytes, study of the nonfilament forms in these diseases should indicate whether their leukopenia is a result of bone marrow inhibition or of excessive white blood cell destruction. However, a disturbance of a leukopoietic mechanism which governed cell maturation, such as has been hypothecated by Fitz-Hugh and Krumbhaar[4] in agranulocytic angina, might result in an increase in the number of young forms present. The differential counts in the following table were made according to the method outlined by Farley *et al.*[3] The total percentage of polymorphonuclear leukocytes is the sum of the nonfilament and filament groups.

Comment. It is obvious that in practically every instance there has been a striking increase in the number of nonfilament forms. In only 2 of the cases of typhoid fever was the initial percentage of nonfilament forms less than 20, and in 11 of the cases it was over 30. The percentage of nonfilament forms in the 2 cases of undulant fever was also markedly increased. In 4 of the cases of typhoid fever there was a moderate leukocytosis which was transitory in 2 instances and probably caused by a bacterial invasion of some tissues other than those of the gastrointestinal tract. The conception of myeloid tissue depression or nonreactivity to stimulation, which is generally offered as explanation of the leukopenia in typhoid fever, does not seem tenable in the presence of the high percentage of young polymorphonuclear cells. In view of the marked and progressive leukopenia the counts in Case J. A. are particularly interesting. This patient was very ill and, were only the total white blood count considered, it would have been said that his infection had overwhelmed the bone marrow. During the early days of his

illness that statement would not have been justified by the nonfilament count; and even in the third week the bone marrow responded well, although not as actively as previously. The patient recovered.

TABLE 1.—FILAMENT AND NONFILAMENT AND DIFFERENTIAL COUNTS (100 CELLS EACH).

Case.	Day of disease.	White blood count.	Nonfilament polys.	Filament polys.	Lymphos.	Monos.	Eosinos.	Basos.
				TYPHOID FEVER.				
C. E.	9	9,500	60	21	18	1	0	0
	16	5,500	29	29	42	0	0	0
R. R.	12	4,300	20	66	14	0	0	0
R. D.	7	5,100	20	60	18	2	0	0
J. D.	13	6,300	36	24	36	4	0	0
F. A.	16	7,300	38	50	12	0	0	0
I. L.	8	5,200	28	30	42	0	0	0
I. K.	14	13,000	36	32	32	0	0	0
	30	8,000	35	30	35	0	0	0
E. L.	9	6,250	13	55	20	12	0	0
J. M.	12	11,500	58	21	17	3	1	0
W. T.	4	6,600	20	52	26	2	0	0
	7	3,200	56	32	10	2	0	0
C. A.	11	6,050	36	28	24	12	0	0
M. S.	6	4,100	30	39	24	7	0	0
A. S.	12	6,600	31	45	15	8	1	0
V. S.	8	11,200	46	25	24	5	0	0
A. C.	8	4,800	64	8	26	2	0	0
S. P.	17	4,050	24	50	16	10	0	0
J. A.	4	3,400	55	13	24	7	1	0
	10	1,950	34	15	49	2	0	0
	17	2,900	8	12	80	0	0	0
	18	3,200	16	26	58	0	0	0
				UNDULANT FEVER.				
E. G.	20	4,850	34	14	48	4	0	0
O. I.	14	4,200	52	30	16	2	0	0

The increase in the nonfilament count in the majority of these cases indicates that the leukopoietic system is responding to severe demands by furnishing immature cells, and suggests that it is a destruction of the white blood cells which is resulting in the leukopenia. In the presence of an increase in the nonfilament forms it does not seem logical to hypothecate that the leukopenia is associated with an inhibition of bone marrow function, but this increase may be due to a disturbance of a mechanism concerned with cell maturation.

Summary. 1. Total white blood cell counts and nonfilament polymorphonuclear neutrophil counts are recorded in 17 cases of typhoid fever and in 2 cases of undulant fever. These show a striking increase in the number of nonfilament, or immature, forms in the majority of instances.

2. The value of the nonfilament form count in the estimation of bone marrow response in these diseases is emphasized.

3. The suggestion is made that the increase in the nonfilament form of polymorphonuclear neutrophilic leukocyte is evidence that the leukopenia in these diseases is associated with white blood cell destruction rather than with bone marrow inhibition; but attention is directed to the possibility that the increase in the number of young forms present may be a result of a bone marrow disturbance which inhibits the maturation of the neutrophils.

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FURTHER NOTE ON A CASE OF GONORRHEAL ENDOCARDITIS WITH RECOVERY.

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In 1930 I[1] reported a case of gonorrheal endocarditis with recovery. The endocarditis began February 17, 1928; the patient was discharged as recovered May 30, 1928. In view of the rarity of recovery in this condition further observations of this patient are deemed worthy of record.

The patient was again seen and examined September 1, 1931. He gave the following history: On his discharge he returned to his home in North Dakota where he attempted little in the way of

physical exertion for 3 months. During this time he gained in strength and at the end of the period he felt quite well. He found that his ability to exercise was normal: he was able to dance, swim, play golf and tramp without heart consciousness or abnormal sensations of any kind. He indulged freely in these exercises. He returned to Washington, D. C., July 14, 1931, weighing 148 pounds. Ten days later he began a lobar pneumonia of the left lower lobe which lasted 5 days, with 2 weeks' convalescence. He lost 16 pounds in weight during this illness. He gradually regained his strength and, when seen September 1, 1931, looked and seemed well.

Examination on this date showed the left border of cardiac dullness in the fifth interspace to be 9 cm., the right border of dullness in the fourth interspace to be 3 cm. Manubrial dullness in the second interspace was $5\frac{1}{2}$ cm. The pulse rate at the apex was 88. The rhythm of the heart was regular, the sounds clear, with the first apical slightly accentuated. At the base the aortic second sound was greater than the pulmonic, but neither was accentuated. In a well localized area in the second interspace at the left of the sternum there was a diastolic murmur which was maximum in the first half of diastole. It could be heard but faintly in the third interspace on the left. In the erect position the murmur distinctly decreased in intensity. The blood pressure was 118 systolic and 80 diastolic.

An electrocardiogram revealed a regular rhythm of a rate of 90 to 100, with *T* waves upright in all leads. The auriculoventricular and intraventricular conduction times were normal. There was slight slurring and notching of the *Q–R–S* complexes in Leads II and III. No axis deviation was shown. A 6-foot film of the heart gave the following measurements: M L, $8\frac{1}{2}$ cm.; M R, $4\frac{1}{2}$ cm.; transverse diameter of the chest, 30 cm.; diameter of the great vessels, 5 cm.

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BUNDLE BRANCH BLOCK; AN ANALYSIS OF 395 CASES.

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After its origin, the cardiac impulse successively traverses the lower parts of the sinoauricular node, the auricular musculature,

the auriculoventricular node, His' bundle and its branches, and the Purkinje network, to reach the ventricular muscle fibers. Disturbances of conduction in each of the above tissues from the sino-auricular node to the Purkinje tissue inclusive, have been described. This paper deals with a series of cases in which electrocardiograms show what is interpreted as an interference with conduction in one of the large divisions of the bundle of His. Especial attention has been given to a "follow-up" study to determine the prognosis in these cases.

Since the early work of Eppinger and Rothberger,[1,2] Lewis[3,4] and Carter[5] there have been many clinical and experimental studies which have extended our knowledge of this condition, 2 of which deserve particular mention.

In 1920 Wilson and Hermann[6] critically reviewed the literature on bundle branch block and reported their own experiments relating to delayed conduction through the bundle branch divisions. They produced right bundle branch block in dogs by cutting the right branch of the His bundle, and then stimulated the right ventricle by single induction shocks. When the stimulus fell between *T* and the following *P*, a typical right ventricular extrasystole was obtained; when the stimulus fell during the latter part of the *P–R* interval or on the first part of *Q–R–S*, the complexes obtained were transitional in form between the extrasystolic complexes and the right bundle branch complexes. These complexes had *Q–R–S* intervals intermediate between those of normal curves and bundle-branch block curves, and *T* deflections transitional in type between those of normal deflection and those seen in bundle branch block. They also reported clinical observations on cases in which there was similar delay of conduction through the bundle branch divisions.

In 1929 Barker, MacLeod, Alexander and Wilson[7] gave confirmation to earlier works[8,9] which purported to show that what had previously been described as right bundle branch block was, in reality, left bundle branch block. In a human heart exposed by pericardiostomy and employing a technique similar to that used by Lewis, various points on the surface of the ventricles were electrically stimulated and the extrasystoles were simultaneously recorded by the usual three electrocardiographic leads. All of the curves from the right ventricle had upward initial deflections in Lead 1 and all those from the left ventricle had downward initial deflections in Lead 1. The change in direction was found to be produced by crossing the interventricular septum and not merely by a more lateral position. They also observed that as the superior aspect of the heart was approached the ventricular complexes in Leads 2 and 3 tended to become higher and toward the inferior aspect they became inverted. The only conclusion was to infer that curves obtained from the right ventricle were of the type previously supposed to be of left ventricular origin, and conversely curves formerly interpreted

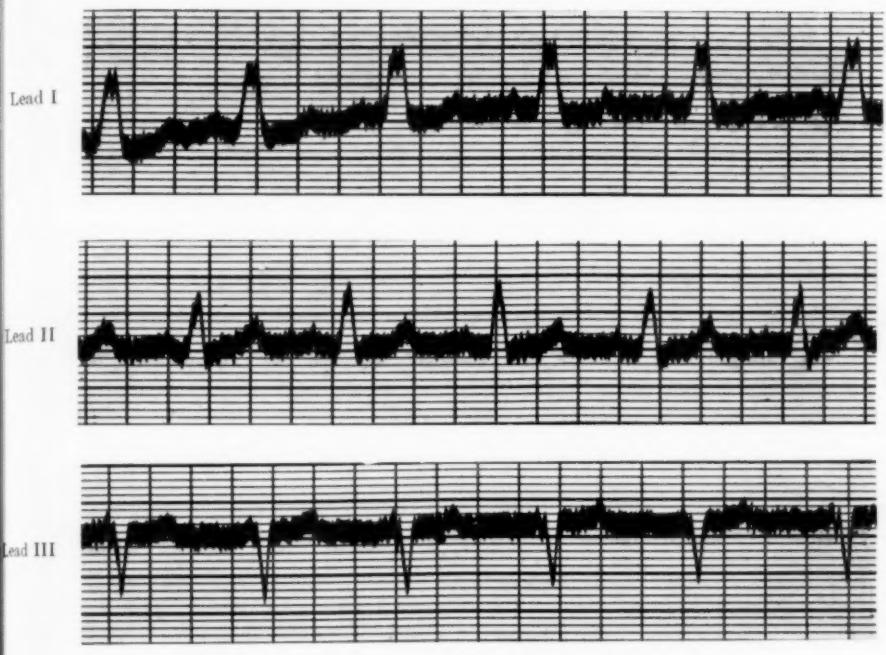

FIG. 1.—Left bundle-branch block—homophasic type.

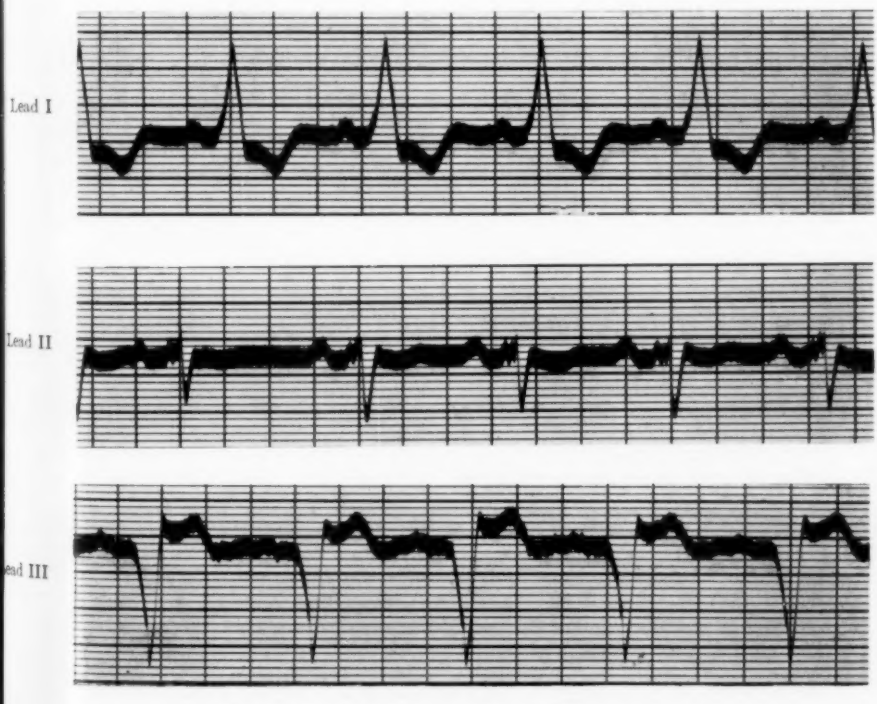

FIG. 2.—Left bundle-branch block—heterophasic type.

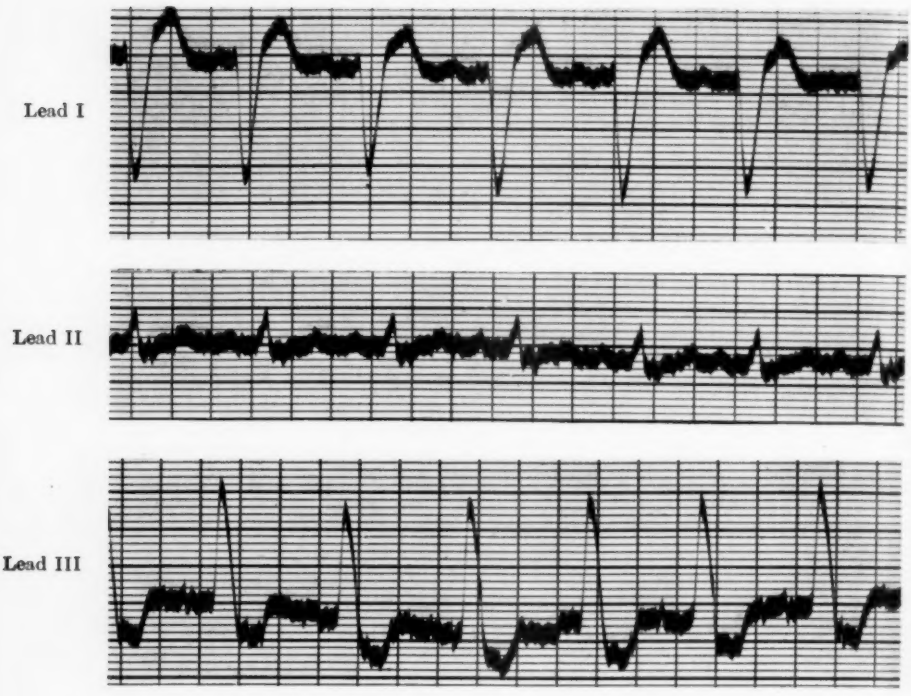

FIG. 3.—Right bundle-branch block—heterophasic type.

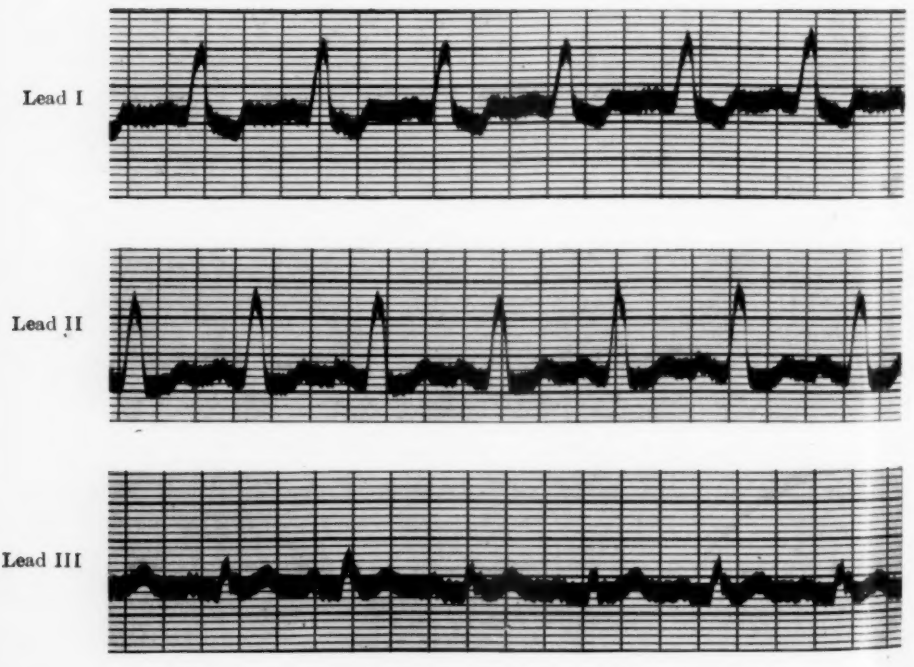

FIG. 4.—Bundle-branch block—indeterminate type.

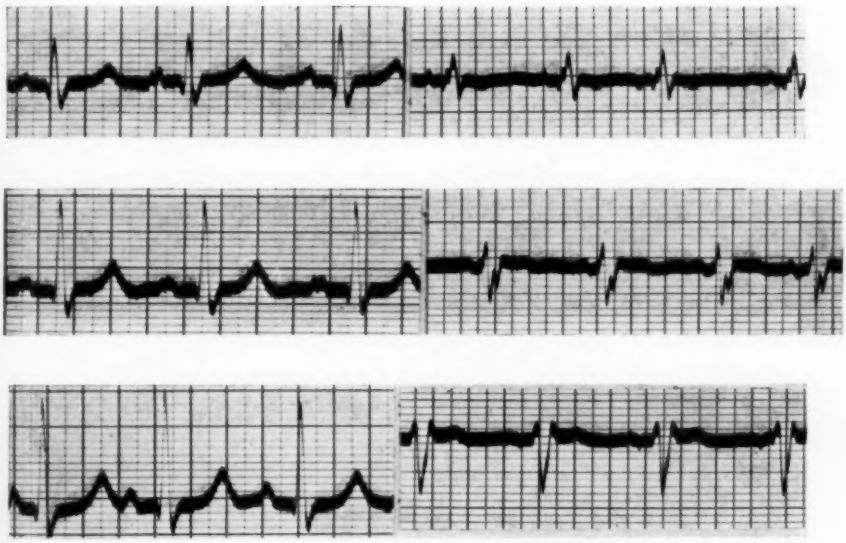

FIG. 5.—Curves showing significant aberration of the ventricular complexes.

as those of right bundle branch block were in reality those of left bundle branch block.

Review of Present Series. *Selection of Cases.* In reviewing over 16,000 electrocardiograms taken in the cardiac clinic of the Massachusetts General Hospital from January, 1915, to February, 1929, we have selected 395 as representing defective conduction through the bundle branches. This work represents an extension of that previously reported in 1923 by White and Viko.[11]

Of these cases 69 per cent were semicharity patients on the general wards or were seen in the outpatient department, while 31 per cent were private patients. The 395 electrocardiograms include those of typical complete bundle branch block, and those transitional in form between complete block and normal conduction, which we believe represent partial block in the bundle branches. Furthermore, we are convinced from a review of recent literature that what has heretofore been called left bundle branch block is in reality right bundle branch block and *vice versa*. With these considerations in mind we have outlined the following classification.

Classification. I*A*. Left Bundle Branch Block—Homophasic Type; so called because the Q–R–S complex and T wave have the same direction in Lead 1. This group fulfills all the criteria of complete left bundle branch block except that the T wave and Q–R–S complex are similarly directed in Lead 1.

I*B*. Left Bundle Branch Block—Heterophasic Type. In contrast to I*A*, the Q–R–S complex and T wave in this group are oppositely directed in Lead 1 The curves in this group fulfill all the classical criteria of complete left bundle branch block.

II. Right Bundle Branch Block—Heterophasic Type. These curves fulfill all the classical criteria of complete right bundle branch block. There were no instances of right bundle branch block with similarly directed Q–R–S complexes and T waves (homophasic) in Lead 1.

III. Bundle Branch Block—Intermediate Type. This group fulfills most of the classical criteria of complete bundle branch block. The Q–R–S is slurred and over 0.1 second in duration. The T wave is often but not always oppositely directed from the Q–R–S complex. The Q–R–S complexes are often similarly directed in Leads 1 and 3, but in no case are they absolutely typical of complete bundle branch block. These curves have been interpreted as partial bundle branch block with conduction sufficiently delayed to result in a Q–R–S complex of over 0.1 second in duration.

IV. Significant Aberration of the Ventricular Complexes (Probably Indicating Slight Degrees of Intraventricular Bundle Branch Block). The Q–R–S wave is usually slurred and notched but its duration is slightly if at all prolonged beyond normal limits. The T wave direction is variable. This group is probably the

early transitional type in which the delay is not marked. That it is associated with serious pathology is evident from the fact that the prognosis in these cases is no better than that in complete bundle branch block.

Cases of marked axis deviation which often give electrocardiograms resembling bundle branch block, have been excluded, as have cases of "functional bundle branch block."

The various data have been compiled separately for each division of the classification and also for the series as a whole, the intention being to make note of any significant differences between the various groups.

Distribution of Cases. Of the 395 cases, 125 were in Group I (26 in I*A*, 99 in I*B*), 29 in II, 81 in III and 160 in Group IV. It was possible to "follow" 308 cases (77 per cent) of which 223 (72 per cent of the 308 followed cases) were found to be dead and 85 alive.

Sex: 301 (76 per cent) were males, and 94 (24 per cent) were females; the sex ratio in the 5 groups was essentially similar.

Age: the age in 360 cases was known. Table 1 shows the age distribution in the 4 groups.

Table 1.—Age Distribution of Bundle Branch Block Cases.

Years.	IA.	IB.	II.	III.	IV.	Total.
0–9	0	0	0	0	1	1
10–19	0	0	1	5	0	6
20–29	0	4	1	3	6	14
30–39	3	4	3	6	6	22
40–49	2	18	5	8	25	58
50–59	9	25	5	25	51	115
60–69	8	23	6	16	48	101
70–79	2	15	3	11	9	40
80–on	0	0	1	1	1	3
	24	89				
Total	113		25	75	147	360

Etiology. While in only a few instances of bundle branch block have localized pathologic lesions been looked for, yet it is generally assumed that the etiology is usually an organic and not a functional disturbance of conduction. This appears true chiefly because this phenomenon is found almost exclusively in old diseased hearts. The cases of functional and intermittent block mentioned above are few in number and such cases are not included in this series. Consequently under etiology of the heart disease in our cases we have put the various factors commonly held to be responsible for heart disease, without the certainty that such disease in any individual instance was responsible for the conduction defect.

In 328 instances a note regarding etiology was made in the record; the results are summarized in Table 2.

TABLE 2.—ETIOLOGICAL FACTORS.

	Left bundle branch block.		Right bundle branch block.	Indeterminate bundle branch block.	Significant aberration.	Total.
	I.A.	I.B.	II.	III.	IV.	
Probable coronary arteriosclerosis	21	65	16	46	90	238
Hypertension	14	43	14	31	52	154
Rheumatism	1	13	6	12	15	47
Syphilis	..	4	1	6	13	24
Myxedema	..	..	..	..	1	1
Subacute bacterial endocarditis	..	..	..	1	1	2
Congenital heart disease	..	..	..	..	1	1
Chronic pericarditis	..	..	..	5	6	11
"Chronic myocarditis"	..	..	..	2	3	8
Acute pericarditis	..	..	..	..	1	1
Aneurysm of aorta	..	..	..	..	2	2

Associated Conditions. *Pulse Rate.* In 23 patients the heart rate was under 50 and in 8 of these it was under 40. In 93 instances the rate was above 90 but in only 5 instances was the heart rate above 120.

Arrhythmias. Table 3 shows the occurrence of associated electrocardiographic abnormalities; they occurred as frequently in patients with partial bundle branch block as in those with complete bundle branch block. The instances of pulsus alternans and gallop rhythm (where such note was made) are included in this table.

TABLE 3.—INCIDENCE OF ARRHYTHMIAS IN CASES OF BUNDLE BRANCH BLOCK.

	I.A.	I.B.	II.	III.	IV.	Total.
Ventricular premature beats	1	16	2	9	17	45
Auricular premature beats	1	7	4	1	4	16
Sinoauricular tachycardia	1	1	..	..	2	4
Auricular fibrillation	2	14	2	13	23	54
Auricular flutter	..	..	..	2	..	2
Paroxysmal auricular tachycardia	1	1	..	..	..	2
Paroxysmal ventricular tachycardia	..	1	..	2	1	4
Auricular standstill	..	..	..	..	1	1
Partial *A–V* block	1	4	3	3	9	20*
Complete *A–V* block	2	2	7	6	..	17
Gallop rhythm	..	4	..	..	2	6
Pulsus alternans	..	5	..	1	3	9
Ventricular escape	..	1	..	..	2	3
S. A. bradycardia and ventricular escape	..	..	..	..	..	1

Structural Cardiac Defects. The heart size was noted in the records of 166 patients. The heart was enlarged in 154 of these 166 patients, Roentgen ray confirming the observation in 145 instances. In 12 cases the heart was of normal size by Roentgen ray. Mitral stenosis was present in 35 patients and 36 showed mitral regurgitation; aortic stenosis was present in 11 and aortic regurgitation in 49. Thirty-one patients had definite coronary occlusion and 2 had aneurysm of the aorta.

Evidence of Functional Insufficiency. Congestive failure was present in 118 cases, angina pectoris in 59, Adams-Stokes syndrome in 12, cardiac asthma in 12, and effort syndrome in 4. Gallop rhythm was noted in 6 cases and pulsus alternans in 9, but these signs were rarely carefully searched for, as White[11] found bundle branch block in 38 per cent of a series of 100 cases of gallop rhythm.

Associated diseased conditions of other organs were those that might be expected in patients of this age group. The more common of these were upper respiratory infections, nephritis, diabetes, arthritis and prostatic disease, in that order of frequency.

Prognosis. The data discussed above were compiled from the clinic and private consultation records. Additional information especially regarding the details of death has not been easy to obtain in most instances, but we were at least able to determine whether the patient was alive or dead in 308 (77 per cent) of the cases.

The prognosis in this series is not that of block of the bundle branches but the prognosis of patients in whom such block was present. It is hard to evaluate the importance of such a disturbance when so many other variables in the way of cardiac and extracardiac disease are present. All we can report is the length of life after bundle branch block was discovered, and that it almost invariably indicates serious organic heart disease.

TABLE 4.—DURATION OF SYMPTOMS IN 308 CASES "FOLLOWED UP."

Group.	Cases.	Average duration of symptoms.	Average known duration of bundle branch block.
I*A*	7 living	5 years, 10 mos.	2 years, 7 mos.
	15 fatal	4 years	3 years, 7 mos.
I*B*	17 living	4 years, 1 mo.	3 years, 1 mo.
	58 fatal	4 years, 5 mos.	1 year, 2 mos.
II	6 living	7 years, 2 mos.	2 years, 5 mos.
	13 fatal	3 years, 2 mos.	1 year, 2 mos.
III	15 living	3 years, 11 mos.	2 years, 8 mos.
	53 fatal	5 years	1 year, 4 mos.
IV	40 living	7 years, 1 mo.	3 years
	84 fatal	3 years, 6 mos.	11 mos.
Entire series	85 living	5 years, 10 mos.	2 years, 11 mos.
	223 fatal	4 years, 1 mo.	1 year, 2 mos.

Table 4 shows the number of cases in each group about whom it was possible to obtain follow-up data. It also shows the average

duration of cardiac symptoms and the average known duration of bundle branch block for both the living and the fatal cases. It should be pointed out that in Group IA the average duration of bundle branch block in the fatal cases would read 1 year and 9 months instead of 3 years and 7 months if 3 quite unusual cases were omitted, also in Group II the average duration of symptoms in living cases would be 3 years instead of 7 years and 2 months if 1 very unusual case were omitted. Otherwise there is a strikingly close similarity of prognosis in each of the 5 groups. From this study it can only be concluded, that as a sign of serious organic heart disease, partial block in one of the bundle branches is equally as serious as complete bundle branch block. The figures compiled for the series taken as a whole are also shown.

With few exceptions the patients still living are either seriously limited in their activity or are actually in some stage of cardiac decompensation. Among the fatal cases the chief cause of death, where this is known, has been, in nearly every instance, cardiac failure.

Summary and Conclusions. 1. An analysis is presented of 395 cases of bundle branch block studied in the cardiac laboratory and clinic of the Massachusetts General Hospital.

2. The diagnosis of bundle branch block can only be made with certainty by the use of the electrocardiograph.

3. From the standpoint of diagnosis and prognosis it is important to determine its presence in cardiac patients.

4. Bundle branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series after the discovery of the conduction fault was 1 year and 2 months but 85 other cases are still alive after an average of 2 years and 11 months following the discovery of the bundle branch block.

5. Partial bundle branch block must be regarded clinically as equally significant with complete bundle branch block, the prognosis in both being essentially the same.

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EVALUATION OF VARIOUS METHODS OF INVESTIGATING THE CIRCULATION IN THE LOWER EXTREMITIES.*

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The importance of studying the circulation has been stressed in numerous contributions during the past few years. Information to be gathered from these studies may be usefully applied in various ways: (1) To detect the presence of impaired circulation early enough to overcome it and permit collateral circulation to develop; this would be of particular value to the diabetic who is notoriously susceptible to arterial changes and gangrene; (2) as a means of making more accurate diagnoses of vascular diseases and distinguishing the vasospastic from the occlusive forms of arterial disease, and (3) it may serve a double purpose when surgical treatment is being considered, not only as to its advisability but may be the final factor in deciding the site of amputation.

There are various methods of studying the circulation. Considerable information may be obtained by questioning the patient and by a physical examination. A history of cramps, coldness, numbness, pains and burning sensations, and a thorough examination of the legs and feet (searching for various lesions[1] such as red spots, scars, scar depressions, or small focal areas of gangrene, pallor, discoloration, coldness, evidences of trophic disturbances, palpation of the pulses, particularly the dorsalis pedis artery, and the presence of sclerosis) will give much information as to whether the circulation is deficient or not.

Some insist that information obtained by a careful examination is sufficient to make satisfactory conclusions of the condition of the circulation. Whether this is so remains to be seen. The objectives of our studies were twofold: first, to determine, if possible, the accuracy of the subjective and objective findings of the physical examination and, second, what can be reasonably expected from the various and more recent methods of studying the circulation.

One hundred and fifty patients were included in this series of studies. Most of them were diabetics. Some were referred for a report on the circulation because they presented clinical pictures suggesting vascular disease. A small group of patients who had no symptoms or signs of vascular disturbances were likewise included.

* Read before the Jefferson Medical College Society for Clinical Investigation, February 25, 1932.

In order to simplify matters and make comparative studies of the various methods, the entire series of patients was divided into two main groups: Series A: those who presumably had a normal circulation, and Series B: those patients who presented evidences of deficient circulation. There were 78 cases in Series A and 72 in Series B.

The following routine of studying the patients was carried out. Observations were made for the presence or absence of lesions, the degree of the dorsalis pedis artery pulsation and evidences of sclerosis, coldness, trophic disturbances, the condition of the veins, and a record of the symptoms usually met with in circulatory disturbances. Oscillometric readings were taken of the feet and legs and the reaction of the skin and capillaries to histamin were recorded at various levels of the feet, legs and lower thighs. These studies were carried out in every case included in the two series. Roentgen ray studies, when possible, were made. The vessels of the legs and feet were examined for evidences of calcification. The intradermal wheal test was performed on a small group of patients, and in some selected cases skin surface temperature readings were made. However, the latter two tests were not employed routinely in the studies. The sphygmotonograph was not available when this investigation was started.

Time and space permit only a brief description of the technique of the various methods employed:

Methods. The *oscillometer* of Pachon[2] was first described in 1909. The apparatus is similar in principle to the sphygmomanometer. It consists of an hermetically sealed metallic box, containing an aneroid capsule, upon which rests the registering needle and an armlet or rubber cuff. The oscillations of the sensitive needle attached to the aneroid capsule will depend upon the site of the extremity studied and the condition of the vessels. To these may be added the condition of the collateral circulation and the blood pressure.

Studies upon normal subjects were carried out by Heitz[3] and Samuels.[4] They found that normal readings at the following sites are: thigh, 4 to 16; upper third of leg, 3 to 12; foot, 0.5 to 2.

The *histamin test* is based on the studies of Lewis[5] on the capillaries and their reactions to various stimuli. The clinical application of Lewis' studies was suggested by Starr.[6] When histamin in a weak solution of 1 to 1000 is inoculated into the skin, a series of reactions take place. These changes are of three types: (*a*) A local dilatation of the capillaries at the site of the trauma or inoculation; (*b*) an erythematous discoloration about the spot due to relaxation of the arterioles, and (*c*) the development of a wheal resulting from the outpouring of plasma through the walls of the vessels. Of these phenomena the most important is the wheal. Normally the wheal should make its appearance and be complete within 5 minutes. The flare likewise appears within 5 minutes. Both the wheal and flare usually become more intense and are more definite at the 10-minute observation. For details of this test and the proper interpretation of the findings, the works of Lewis and Starr are recommended. Takats[7] suggested in a recent contribution that the histamin solution be injected intradermally in order to insure more uniform reactions.

Calorimetric methods of studying the circulation in the extremities are determined chiefly by studying the amount of heat loss in a given time and by skin temperature observations. The latter method is preferable. Brooks and Jostes[8] suggested a method of studying the skin surface temperature by means of an electrical apparatus consisting of a thermocouple and a galvanometer. These principles were amplified and modified by Scott[9] and McGlone,[10] thereby giving us apparatuses which are more practical for clinical use. These instruments are particularly valuable in the differential diagnosis of arterial diseases and when decisions have to be made as to the advisability of surgical procedures to correct the impaired circulation and to determine what improvement may be expected from these operations. This method of study has been favorably commented upon by Allen and Smithwick,[11] Brown,[12] Adson,[13] White[14] and others.

In patients who have deficient circulation, the problem of arteriospasm or mechanical occlusion of the lumen must be solved. On such occasions *skin surface temperature studies* are exceedingly helpful. Readings are taken before and after nerve block. The pressor or vasoconstrictor stimuli may be blocked either by spinal or general anesthesia and local infiltration of the nerves to the parts about to be studied. When this is accomplished, there is normally a rise of several degrees, depending upon the type of anesthesia and room temperature. This reading is known as the vasodilatation level and suggests that the spasm of the vessels has been overcome. When the skin temperature fails to reach the normal level, we assume that there is some mechanical obstruction to the arterial circulation. The difference between the highest skin temperature after nerve block and the normal vasodilatation level is termed the "obstruction" or "occlusion" index.

The value of the occlusion index becomes apparent when we are considering ganglionectomy or ramisectomy. If, for example, there is no rise in the skin surface temperature after 20 to 30 minutes following nerve block, we may conclude that the benefits from this operation are so slight that the procedure is not indicated. However, if the occlusion is only partial and the index is about 2, this suggests that the deficiency of the circulation is probably due to vasospasm and that improvement of the circulation may be expected from surgery.

Intradermal injections of salt solution were employed by McClure and Aldrich[16] as a means of studying edema. Cohen[17] and Stern[18] suggested this test for determining the efficiency of the circulation in arterial disturbances. Briefly, the technique is as follows: 0.2 cc. of 0.85 per cent salt solution is injected intradermally at various levels of the extremity. The wheals produced by these injections are observed until they disappear. The time required for absorption of the fluid is determined by palpation and not by visual judgment. Normally, the disappearance time is 60 minutes. Readings of 5 to 10 minutes for disappearance time are usually found in areas adjacent to gangrene and readings between 10 and 20 minutes suggest a deficient circulation.

Roentgen ray studies of the vessels consist of the usual flat-plate roentgenograms giving us information upon the condition of the arteries, particularly for evidences of calcification. This is discussed more fully hereinafter when evaluating the various methods.

Bloodvessel visualization by injection of opaque solutions into the larger arteries prior to the Roentgen ray examination has been employed by Greenbaum and Carnett.[19] This method, a procedure requiring surgical technique, can only be done in a hospital, and its field of usefulness is too limited to warrant promiscuous employment.

The *sphygmotonograph* or recording sphygmomanometer is based upon the same principle as the oscillometer. Simpson,[20] and Pearse and Morton[21] were favorably impressed with it. They claim that it has the added advan-

tage of giving accurate and permanent records of the circulation. Unfortunately, this instrument was not available when our studies were being carried out. The author is in no position to compare it with the other methods of study.

Comment Upon Method of Grouping. Of the above mentioned methods of study, the oscillometer and histamin tests were carried out in every one of the 150 patients. The symptoms, physical signs, and a search for lesions were recorded. Roentgen ray examinations were made when possible.

The studies and observations of every case were so recorded that statistical data would be available after a sufficient number of patients had been investigated. The studies included a careful physical examination and the above mentioned oscillometer and histamin tests and Roentgen ray. This information was recorded upon a form illustrated below.

The studies were reviewed in each case and the decision of classifying them as deficient or of ample circulation function was made. The problem of grouping the patients into the two series was not difficult when the results of the tests were uniformly positive or negative, but there were occasions where all the tests did not tally. In these cases the decision rested with the final outcome of the case, that is, if the major tests indicated good circulatory function and gangrene developed in the patient under observation, he was classified in the pathologic group or Series B. Patients who showed evidences of good circulatory function with the tests, who had little or no symptoms and signs but showed calcification of the vessels through the Roentgen ray, were placed in Series A, the efficient circulatory group. This will be discussed in detail when evaluating the different methods.

Some of the case records of the two groups have been arranged in tabular form to illustrate the method of classifying the results of the studies.

The arrangement of Table 2 is self-explanatory. Six records of each series are depicted. The symptoms and signs are charted + when present or positive, ⊕ when doubtful or indefinite, and ○ when absent. When symptoms and signs were intense ++ was used. Under the column for veins, a single + indicated varicosities, and ++ was employed when thrombophlebitis was present. The same method was employed for charting results of the tests. Normal oscillometric readings and histamin reactions are indicated by ○. When the oscillometer gave subnormal readings or the reaction was delayed, suggesting deficient circulation, the + sign was used; ++ was recorded if the oscillometric readings were zero or if the histamin test showed marked delay.

Some of the records were included in the table to illustrate the difficulty which presents itself when attempting to classify them. As an example of this problem, consider Case B-6. The good pulse,

TABLE 1.—FORM OF RECORDING RESULTS OF THE TESTS AND EXAMINATION OF (A) NORMAL CIRCULATION FUNCTION AND (B) DEFICIENT CIRCULATION.

Record of Patient With Efficient Circulation: Series A.

No.: 13-A Name: J. R. Age: 51 Female Blood pressure: 140/80

History:

Cramps	0
Coldness	0
Numbness	0
Pains	0
Burning sensations	0

Examination:

	R.	L.
Coldness	0	0
Pulsations:		
Dorsalis pedis	Good	
Popliteal		
Femoral		
Phlebitis; thrombophlebitis	+	+
Sclerosis	0	0

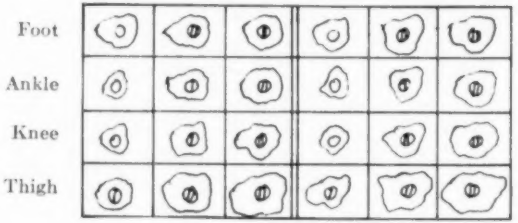
Lesions:

	R.	L.
Red spots	0	0
Blebs	0	0
Scars	0	0
Scar depressions	0	0
Ulcerations	0	0
Focal gangrene	0	0

Oscillometer Readings:*

Pressure	Leg. R.	Leg. L.	Foot. R.	Foot. L.
160	10	12	2	2
140				
120	12	11	1½	2
100				
80	8	6	1½	2
60				
40				

Histamin Reaction:†



Roentgen ray examination:

No evidences of calcification in the vessels of the legs or feet.

Record of Patient With Definitely Impaired Circulation: Series B.

No.: 70-B Name: M. K. Age: 60 Female Blood pressure: 140/76

History:

Cramps	+
Coldness	+
Numbness	0
Pains	++
Burning sensations	0

Examination:

	R.	L.
Coldness	+	+
Pulsations:		
Doralis pedis	Diminished	
Popliteal		
Femoral		
Phlebitis; thrombophlebitis	+	+
Sclerosis	+	

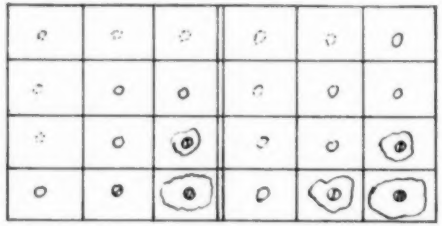
Lesions:

	R.	L.
Red spots	0	0
Blebs	0	0
Scars	+	+
Scar depressions	+	+
Ulcerations	0	0
Focal gangrene	+	0

Oscillometer Readings:*

Pressure	Leg. R.	Leg. L.	Foot. R.	Foot. L.
160	1	1½	0	0
140				
120	1	2	0	0
100				
80	1½	2	½	0
60				
40				

Histamin Reaction:†



Roentgen ray examination:

Evidences of sclerosis of the vessels of the legs and feet.

* Oscillometer: Readings show the degrees of oscillation at the different pressures. The maximum figures give the status of the circulation in the extremity.

† Histamin reaction is interpreted according to the appearance of the wheal and flare as suggested by Starr.

absence of coldness to the part, and negative Roentgen ray findings would suggest that this record belongs to the nonpathologic group. However, the circulatory function tests, both the oscillometer and histamin, definitely pointed to a deficient circulation. The contradictory findings suggest that the decision would rest with the ultimate outcome of the condition of the leg and further search for more clinical data. Lesions were present on the leg. Gangrene subsequently developed and amputation had to be performed in order to combat the toxemia which was progressively getting worse. Examination of the vessels of the amputated limb showed advanced arterial disease, thereby proving that the tests for circulatory function were helpful in pointing out the existence of impaired circulation despite the negative Roentgen ray and the lack of physical findings.

In Cases A-75 and A-77, conditions were reversed. The Roentgen rays showed evidences of calcification, but the tests were negative on all counts. The clinical background was one of normal or efficient circulatory function. Such cases were listed in Series A because the evidence, despite the Roentgen ray finding of calcification, was decidedly in favor of good circulatory function.

Discussion of Results and Evaluation of the Tests.—The data obtained from the records of the two series of patients were arranged in tabular form for statistical purposes and comparison. This information can be studied in Table 3:

Oscillometric Readings. In the group with good circulatory function, the oscillometric readings of the legs were within normal limits in 76 of the 78 cases (97.4 per cent). In the feet, normal readings were observed in 56 cases (71.8 per cent) and in 22 cases (28.2 per cent) the readings were below normal.

In Series B (the pathologic group) 49 cases (68 per cent) had subnormal readings in the legs, and in 23 cases (32 per cent) the readings were normal. Readings of the feet showed that 65 cases (90.3 per cent) were below normal and only 7 cases (9.7 per cent) had normal figures.

Briefly, the oscillometer seems to have given satisfactory or acceptable results in the efficient group (76 out of 78 cases), but failed to maintain the satisfactory percentage in the pathologic group, where only 68 per cent of the cases showed subnormal readings.

The interpretation of the findings in the pathologic group demands some discussion. At first glance one may assume that the oscillometer has failed to give us accurate information, since only 68 per cent showed evidences of deficient circulation, and therefore should be discredited as a test for circulatory function. A survey was made of the remaining 32 per cent of the patients who had good oscillometric readings despite the fact that they were classified in the pathologic group. A majority of this group had an increased blood pressure. There were no references in the literature to guide

TABLE 2.—SHOWING SOME OF THE RECORDS IN SERIES A (EFFICIENT CIRCULATION) AND SERIES B (IMPAIRED GROUP).

Case No.	Name.	Age.	Sex.	Symptoms.					Physical examination.					Oscillometer.		Histamin.		Roentgen ray.	Blood pressure.		Diagnosis.
				Cramps.	Coldness.	Pain.	Numbness.	Burning.	Pulse.	Sclerosis.	Coldness.	Lesions.	Veins.	Legs.	Feet.	Legs.	Feet.		Systolic.	Diastolic.	
A-1	R. B.	62	F	0	0	0	0	0	Pres.	0	0	⊕	0	0	0	0	0	....	134	88	Diabetes
A-14	E. L.	43	F	+	0	0	⊕	0	Pres.	⊕	0	0	0	0	0	0	0	Neg.	142	80	Thyroid
A-29	R. K.	50	F	0	0	0	0	0	Pres.	⊕	0	0	0	0	0	0	0	Neg.	130	80	Diabetes
A-26	C. W.	42	F	0	+	0	0	0	Pres.	0	+	⊕	++	0	0	0	⊕	Sl. deposits	130	90	Diabetes
A-75	C. C.	50	M	0	+	0	0	0	Good	0	+	0	0	0	0	0	0	Calcif.	150	80	Diabetes
A-77	R. J.	59	F	0	0	0	0	0	Good	0	0	0	++	0	0	0	0	Calcif.	170	100	Diabetes
B-6	M. B.	48	M	++	0	+	0	0	Good	0	0	++	0	+	++	++	++	Neg.	130	70	Diab.; gangr.
B-8	M. F.	58	F	0	++	+	+	+	Good	+	+	++	0	+	++	⊕	+	Calcif.	170	98	Diab.; threat. gangr.
B-16	M. K.	61	F	+	+	+	0	0	Abs.	+	+	+	0	+	++	+	++	Calcif.	140	76	Diab.; gangr.
B-34	L. S.	60	M	+	0	0	0	0	Good	0	0	++	0	0	0	+	+	Calcif.	120	70	Diab.; gangr.
B-76	C. S.	54	M	+	+	0	0	0	Abs.	+	+	+	+	+	++	0	0	Calcif.	140	78	Diabetes
B-56	M. Z.	60	M	0	+	0	0	0	Dim.	+	+	+	0	++	++	+	+	Neg.	134	74	Diab.; threat. gangr.

0 = Negative or normal. + = Positive findings. ⊕ = Questionable or suggestive.

TABLE 3.—ANALYSIS OF THE 150 CASES: SHOWING COMPARATIVE FREQUENCY OF THE SYMPTOMS AND SIGNS WITH THE RESULTS OF THE VARIOUS TESTS.

	Symptoms.					Physical examination.					Oscillometer.		Histamin.		Roentgen ray.
	Cramps.	Cold-ness.	Pain.	Numb-ness.	Burn-ing.	Pulse.	Sclero-sis.	Cold-ness.	Lesions.	Veins.	Legs.	Feet.	Legs.	Feet.	
Series A (78 cases)	+ 18 ++ 3 ⊕ 8	+27	+ 16	+ 8	+ 6	G 61 D 6 ⊕ 11	+ 6 10	+ 22	+ 13 7	+ 8 ++15	+ 1 ⊕ 1 ○ 76	+ 11 ++ 2 ⊕ 9 ○ 56	+ 1 ○ 77	+ 8 ⊕ 14 ○ 56	+ 9 N.M. 30 ○ 39
Totals . . .	29	27	16	8	6	G 61 D, ⊕ 16	16	22	20	23	○ 76 +, ⊕ 2	○ 56 +, ⊕ 22	○ 77 + 1	○ 56 +, ⊕ 22	○ 39 + 9
Series B (72 cases)	+ 34 ++ 8	+42	+ 35 ++ 8	+15	+ 6 ++1	G 19 D 22 4 A 27	+55 1	+ 53 ++ 4	+ 40 ++12 5	+ 7 ++14	+ 35 ++12 ⊕ 2 ○ 23	+ 20 ++41 ⊕ 4 ○ 7	+ 34 ++ 6 ⊕ 13 ○ 19	+ 38 ++16 ⊕ 11 ○ 6	+ 51 N.M. 9 ○ 12
Totals . . .	42	42	43	15	7	A 27 D, ⊕ 26 G 19	56	57	57	21	○ 23 +, ⊕ 49	○ 7 +, ⊕ 65	○ 19 +, ⊕ 53	○ 6 +, ⊕ 65	○ 12 + 51

+ Present
++ Intense
⊕ Vague, indefinite

G Good
D Diminished
A Absent

○ Normal
+ Diminished
++ Markedly diminished
⊕ Questionable

○ No calcif.
+ Calcif.
N.M. Not mentioned

us upon the question, but in our experiences hypertensives usually gave high oscillometric readings, and it is quite possible that the increase in pressure sends the blood through with greater force and gives good readings despite pathologic changes in the arteries. However, this need not apply in every case because there were occasions where the oscillometer showed subnormal readings in patients who had hypertension.

Another factor for consideration is the influence of the collateral circulation upon the readings. Since the mechanism of the oscillometer is so arranged as to give us information upon the gross bloodflow and the rhythmic expansion and contraction of the vessels, it is only fair to assume that if a satisfactory collateral circulation has been established, we may get normal readings despite the presence of definite disease in some of the vessels. These facts are presented for consideration and may explain some of the failures of the test to conform with the clinical findings. Recently, de Takats[22] mentioned the possibilities of the oscillometer in determining the existence of an attempt to produce adequate collateral circulation.

The value of the oscillometric readings in the feet will be considered separately. In Series A, the readings were normal in 56 cases (72 per cent) of the 78, and in the remaining 22 cases (28 per cent) they were subnormal. The 72 per cent normal readings in the feet seem to be rather disappointing when the figures are compared with the excellent record of 97 per cent normal readings of the legs in the same group, Series A. In the pathologic group, Series B, observations on the feet showed that 65 cases (90.3 per cent) of the 72 had subnormal readings.

How are we to explain the 28 per cent subnormal readings in the feet of the presumably normal group, Series A? Is it because the instrument fails to give satisfactory results when studying the circulation in the feet or is it possible that there are either anatomic differences in the circulation or that early pathologic changes are taking place without apparent or perceptible manifestations?

Attempting to settle this question, it may be pertinent to mention that the skin surface temperature of the toes and soles even under normal conditions is several degrees below the temperature of other parts of the body. This finding lends itself to the thought that there may be some anatomic condition as a result of which the circulation in the feet does not keep pace with other areas. This contention is further supported by the fact that the same discrepancy between the leg and foot percentages were noticed in the statistical studies of the histamin reaction.

To summarize the merits of the oscillometer, it is an instrument which measures the degree of pulsation of the vessels in that particular area. It removes the arbitrary personal equation when the presence or absence of a pulse is under consideration. It permits

us to confirm information of the circulation gathered by physical examination, which may be misleading in a certain percentage of the cases. It may indicate the establishment of a collateral circulation in a limb with definite disease of the vessels. Normal oscillometric readings are particularly significant when they confirm a negative clinical background, that is, absence of signs, normal histamin response, and a negative Roentgen ray. A diagnosis of an efficient circulation in such cases is warranted.

Low oscillometric or zero readings almost invariably point to some impairment of the circulation. This suspicion is further strengthened if the various symptoms and signs are present and the histamin test shows a retarded or delayed response. The oscillometer, however, does not help us in determining whether the deficiency in circulation is due to a spasm of the vessel or to mechanical causes.

Normal readings may be found in some cases where the evidence points to pathologic changes in the vessels. Hypertension and the existence of a sufficient collateral circulation are offered as possible explanations on such occasions.

Histamin Reactions. The results of this test on the legs was normal in 77 out of the 78 cases (98.7 per cent) in Group A (the series of normal patients). In the feet the results were not so satisfactory; 56 patients showed a normal reaction, a percentage of 71.8 per cent and in 22 cases (28.2 per cent) the reaction was delayed. In Series B, the pathologic group, 53 cases out of 72 had a delayed reaction and, in 19 cases, the reaction was normal (73.6 per cent and 26.4 per cent respectively).

The best results were obtained in the normal group. In the pathologic series a good response to histamin was found in 26.4 per cent of the cases. Again, the question of reliability of the test is raised. The same arguments hold true for the histamin test as were offered for the oscillometer, particularly the possibility of the establishment of a satisfactory collateral circulation. The fact that in 13 of the 19 patients the normal response to histamin was confirmed by normal oscillometric readings is sufficient argument against condemning these tests and against deciding that they fail to detect pathologic conditions. On the contrary, may we not assume that their results strongly suggest that an efficient collateral circulation has taken over the burden of supplying the tissues in these extremities?

The results of the histamin reaction when investigating the circulation in the feet showed practically the same percentage as those obtained with the oscillometer. The discussion of the discrepancies of the oscillometric findings in the feet may be applied to the histamin test. Further comment upon the variations would be mere repetition.

A comparison of these two methods of study is arranged in Table 4:

TABLE 4.—COMPARATIVE FIGURES AND PERCENTAGES OF OSCILLOMETRIC READINGS AND HISTAMIN REACTIONS.

	Series A (78 cases).				Series B (72 cases).			
	Normal.		Below normal.		Normal.		Below normal.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Legs:								
Oscillometer	76	97.4	2	2.6	23	32	49	68
Histamin	77	98.7	1	1.3	19	26.4	53	73.6
Feet:								
Oscillometer	56	71.8	22	28.2	7	9.72	65	90.3
Histamin	56	71.8	22	28.2	6	8.33	65	90.3

Summarizing the merits of the histamin reaction, a prompt normal reaction is indicative of a satisfactory peripheral circulation. It may be looked upon as a guide for the condition of the capillaries and peripheral circulation and gives us information indirectly as to the status of the deeper and larger vessels. This information may be of value in determining whether there is sufficient or ample blood supply to that extremity. It may indicate the presence of an adequate circulation when dealing with pathologic extremities. This information may be of value in determining the site for amputation in selected cases.

Whether or not the histamin reaction test is superior to the oscillometer is not easily decided. The comparative figures in Table 4 seem to be slightly in favor of the histamin test. This slight advantage may be counterbalanced by the fact that the element of personal equation enters in the interpretation of the results and in the technique. Judging from Table 4, one can see that the two tests employed have practically similar percentages. When the oscillometer checks up with the clinical picture, almost invariably the histamin shows the same result. When one test does not confirm the clinical picture, as a rule the other gives a similar result. When the histamin test and the oscillometer indicate good function or a deficient circulation, experience has taught us to accept their findings regardless of the results of the Roentgen ray or the presence of some isolated symptoms or signs.

Discussion of the Significance of the Various Accepted Symptoms and Signs in Deficient Circulatory Function. An analysis of the incidence of these symptoms was made in both series. The results are arranged in Table 5:

TABLE 5.—FREQUENCY AND PERCENTAGES OF SYMPTOMS IN GROUPS A AND B.

	Series B (72 cases). (Pathologic.)		Series A (78 cases). (Efficient.)	
	Cases.	Per cent.	Cases.	Per cent.
Cramps	42	58.3	29	37.0
Coldness	42	58.3	27	34.6
Pains	43	59.7	16	20.5
Numbness	15	20.8	8	10.2
Burning	7	9.7	6	7.6

Glancing over the table, one is impressed not only with the comparatively low percentages of such prominent symptoms as cramps, coldness and pains in the pathologic group but also their unexpected frequency in the series of patients with efficient circulation.

An analysis was made of the 42 patients in the pathologic group who complained of cramps. As a rule, this symptom is accompanied by one or more of the other complaints. In 6 cases, cramps were the only complaint. Similarly, in 36 of the 42 patients there were other physical evidences of deficient blood supply.

The circulatory function tests showed an impaired circulation in 31 of the 42 patients.

In Series A, the efficient group, there were 29 patients (37 per cent) who complained of cramps. The absence of the more complete combination and array of symptoms and signs was apparent. Although coldness of the part was also present on examination in 17 of the 29 cases, the physical signs failed to point definitely to impaired circulation. The circulatory tests likewise failed to confirm any suspicions of deficient circulation in 27 out of the 29 cases. Eighteen of this group were Roentgen rayed; in 15 cases there were no evidences of calcification.

From the above analysis we may conclude that such symptoms as cramps, coldness and pains appearing in one combination or another are significant when they are confirmed by the various tests for circulatory function. While single symptoms may cast suspicion upon the efficiency of the circulation, they often fail to receive adequate support from the other methods of study. This is particularly true with such symptoms as coldness of the feet and a history of pain which may be vague and, in many instances, may be attributed to some orthopedic condition or to neuritis.

Discussion of Results and Significance of the More Prominent Signs Found in Circulatory Disturbances. In the course of the physical examination, the following findings were emphasized: (*a*) The degree of pulsation of the dorsalis pedis artery, whether absent, questionable, diminished or good; (*b*) evidence of sclerosis to the palpating finger; (*c*) coldness; (*d*) the lesions mentioned above in the introductory remarks, and (*e*) the condition of the veins. The relative frequency and percentage of the various signs are arranged in Table 6:

TABLE 6.—INCIDENCE AND PERCENTAGES OF THE SIGNS IN THE TWO GROUPS.

	Series A (78 cases). (Efficient circulation.)		Series B (72 cases). (Pathologic group.)	
	Cases.	Per cent.	Cases.	Per cent.
Pulse:				
Good	61	78.2	19	26.3
Questionable	6	7.6	4	5.0
Diminished	11	14.2	22	30.5 †
Absent	..	..	27	37.5 †
Sclerosis:				
Present	6	7.6	57	79.1
Suggestive	10	12.8		
Coldness: Present	22	28.2	57	79.1
Lesions:				
Present	13	16.6	52	72.2
Suggestive	7	8.9	5	6.0
Veins:				
Varicose	8	10.2 *	7	9.7 ‡
Thrombophlebitis	15	19.2 *	14	19.4 ‡

* 23 (29.5 per cent). † 49 (68 per cent). ‡ 21 (29.1 per cent).

(*a*) *The dorsalis pedis pulse* seems to be the main objective when one is searching for information concerning the circulation of the feet. It is easily found on the outer aspect and running parallel to the first metatarsal bone. It is superficial and can be rolled by the palpating finger, thereby giving us some information as to the presence or absence of sclerosis.

A good pulse was noticed in 61 cases (78.2 per cent) in Series A; in 6 patients the pulse was diminished, and in 11 patients the pulse was questionably diminished. One may expect to find a certain percentage of presumably normal patients with some diminution of the pulse. However, the pathologic group showed that *in* 19 *patients* (26.3 *per cent*) *there was a good dorsalis pulse.* The relatively high percentage of good pulsation in patients who have definite evidences of arterial disease is sufficient ground *to question the reliability of this sign as a guide for studying the circulation.* It may be of interest to mention that among the 19 patients with good dorsalis pulsation, there were 3 patients with diabetic gangrene, 3 with threatened gangrene, 1 with a trophic ulcer, and 1 patient had arteriosclerosis with claudication. Although in some cases of diabetic gangrene a good pulse may be explained by our more modern conception of the pathogenesis of gangrene along the lines of deep infection and mechanical interference of the local blood supply, nevertheless we must take cognizance of the fact that a good pulse may give us a false sense of security.

(*b*) *Sclerosis* of the dorsalis pedis artery was found in 57 patients (79.1 per cent) in the pathologic group, and in 6 cases (7.6 per cent) of the presumably normal group, Series A. Its presence signifies that changes have taken place in the arteries and further investigation with circulatory function tests and Roentgen ray studies are warranted. The finding of sclerosis and its value as a guide to

circulatory function is questionable. It does not necessarily prove that all the vessels are similarly involved, and the always existing question of an adequate collateral circulation having been established, must be kept in mind.

(*c*) *Coldness* was found in 57 cases (79.2 per cent) of the pathologic group, but was also present in 22 of the efficient circulation series (28.2 per cent). Although its high incidence in the pathologic group is similar to the frequency of sclerosis, one hesitates to attach the same importance and significance to this finding because it is more or less common and is met with in too high a percentage among the normals.

(*d*) *Lesions.* The variety of lesions which may be found in the lower extremities, and their significance, were discussed in detail in a previous publication. They were found either singly or in combination. The presence of these lesions indicates that pathologic changes have taken place in the smaller vessels and indirectly suggest involvement of the larger arteries. Such individuals may be labeled as potential cases of gangrene. The importance of their early recognition is obvious.

(*e*) *Veins.* Changes in the veins in the form of varicosities or thrombophlebitis were found in 23 cases (29.5 per cent) in Series A, and 21 cases (29.2 per cent) in the pathologic group, Series B. Although it is possible that infection in the veins may ultimately have some influence upon the condition of the arteries, as in Buerger's disease, the similar percentages in both groups fail to establish this possibilitity as a factor in determining the status of the circulation. However, the number of patients with varicose veins observed in these studies is too small to warrant any conclusions.

Roentgenographic studies were carried out in 111 patients; 48 in Series A and 63 in Series B. In the pathologic group (Series B), 51 cases (81 per cent) out of the 63 showed evidences of calcification; in 12 cases (19 per cent) there were no evidences of disease noted in the vessels despite the fact that the history, physical examination and the circulatory tests all indicated a deficiency of the circulation.

The records of these 12 cases were examined in an effort to learn why the Roentgen ray reports were negative when all the evidence pointed to the presence of a pathologic condition. In this group were found cases of Raynaud's disease, thromboangiitis obliterans, acute thromboarteritis, embolic occlusion and 8 diabetics, 4 of whom had threatened gangrene. In Raynaud's disease and embolic occlusion the vessels in the involved area may be perfectly normal, the seat of the trouble being higher up; the Roentgen ray therefore cannot be expected to offer us any assistance. In Buerger's disease the underlying lesion is one of inflammation, chronic and insidious in character, and the value of Roentgen ray in making the diagnosis is questionable. Samuels[23] noticed that in many cases of thromboangiitis obliterans the Roentgen ray findings are negative, unless

this condition develops in older patients who have arteriosclerosis, in which event the roentgenogram may show evidences of calcification.

In diabetics who have a tendency to develop atheromatous changes in the vessels with a resulting deficiency in circulation, it is a question whether Roentgen ray examination can detect this pathologic condition of the arteries.

The results in the efficient circulation group showed 39 cases with negative findings and 9 cases with evidences of calcification. Of the 9 cases with calcification, 8 had a good dorsalis pedis pulse and the circulatory function tests showed an efficient circulation in practically all of them.

It would seem that the attitude to assume in these cases is that the Roentgen ray gives us information as to the presence or absence of calcification, the degree of calcification, and what vessels are involved. However, it is important for one to have a clear idea that calcification of an artery is one thing and that the status of the circulation of this vessel is another. The presence of sclerosis and calcification does not necessarily mean that the circulatory function has been definitely impaired. Then again we must remember that even in extensive arteriosclerosis there may have been established an adequate collateral circulation with a satisfactory blood supply to the parts. This may explain the good results of the circulatory function tests in some cases of arteriosclerosis.

Summary. The importance of studying circulatory function in the extremities is stressed. The various methods of investigating the status of the circulation in the lower extremities have been enumerated and analyzed.

The suggestion that the ordinary methods of careful history taking and a thorough physical examination will yield sufficient and satisfactory information is questioned.

The symptoms and signs of deficient circulation were studied in 150 patients. Oscillometric readings and the reaction of the capillaries to histamin were observed in each patient. Roentgen ray examinations of the vessels were made in 111 patients of the series.

The cases were placed in two groups: Series A, including the 78 cases where the circulation was found to be efficient and presumably normal, and Series B, with 72 cases, where evidences of impaired circulation were found.

Evaluation of the individual tests proved difficult and the conclusions must necessarily be more or less arbitrary. However, one may get some comprehensive idea of what may be expected of these methods of investigation.

Conclusions. The merits and failures of the various methods of study appear to be as follows:

The *oscillometer* measures the degree of pulsation of the vessels in a particular area without personal equation as an arbitrary factor

in determining results. It gives information about the deeper vessels which cannot be palpated. It may suggest the existence of collateral circulation when definite lesions of the vessels are apparent. In some cases, hypertension may give higher readings. It compares favorably with other accepted methods of testing circulatory function.

The readings in the legs in Series A were most satisfactory (97.4 per cent of the efficient circulation group were normal). In Series B, the pathologic group, the oscillometer indicated a deficient circulation in 68 per cent of the cases, while the remaining 32 per cent had normal readings. Hypertension and an adequate collateral blood supply may account for many of the good results of the circulatory function tests in the pathologic group.

The reaction of the capillaries to histamin indicates the condition of the superficial circulation and indirectly of the deeper vessels. It may be employed as a guide to the capillary circulation and nutrition of the tissues. This information may be of practical value to the surgeon when considering the site for amputation. It is also a good guide in determining the status of the circulation. In this respect it ranks with the oscillometer in value. In the efficient circulation group, Series A, the histamin reaction in the legs showed a normal result in 77 cases out of 78 (98.7 per cent). In the pathologic group, delayed reactions were found in 73.6 per cent of the cases. The discrepancy is explained on the basis of the successful establishment of collateral circulation.

The outstanding *symptoms* such as cramps, coldness, pains, numbness and burning are analyzed relative to their frequency and significance. Cramps and coldness are mentioned as complaints in 42 cases (58.3 per cent) in Series B, but were also found in 37 and 34.6 per cent respectively in the efficient circulation group. Pain was recorded in 59.7 per cent of the pathologic group and in 16 cases (20.5 per cent) in Series A. Symptoms, particularly when two or more are present, may suggest circulatory disturbances, but these suspicions must be confirmed by the various tests for studying the circulation.

Physical examination of the extremities may throw some light upon the status of the circulation by ascertaining the dorsalis pedis pulse, palpating for sclerosis as well, noting the warmth or coldness of the foot, searching for various types of lesions and the condition of the veins. A good pulse is a welcome sign but may give misleading information as to the exact condition of the other vessels. Similarly, the presence of sclerosis need not necessarily mean that the circulation is impaired.

Roentgen ray studies in 111 patients of the 150 showed evidences of calcification in 51 cases out of 63 (81 per cent) in Series B, the pathologic group, and in 12 cases (19 per cent) the findings were

negative. In the efficient circulation group, out of 48 cases studied, 39 were negative and 9 showed calcific deposits in the vessels.

The possibility of good circulation function existing despite evidences of calcific deposits in the vessels is discussed. It is questionable whether the Roentgen ray will reveal early atheromatous changes in diabetic vessels and the inflammatory changes in Buerger's disease.

Conclusions. The usual symptoms and signs that one expects to find in patients with impaired circulation are often unreliable. When they are present in combination, circulatory disturbances may be suspected. However, in order definitely to establish the diagnosis of arterial disease, the various circulatory tests should be employed.

All of the newer methods of study have merit. Some are more practical than others and may be more readily applied. The oscillometer and the capillary response to histamin are especially valuable in determining the status of the circulation, particularly to exclude pathologic conditions, and are fairly good guides in determining the presence of an efficient collateral blood supply.

Skin surface temperature studies are of value in distinguishing the vasospastic from the occlusive form of arterial disease.

Information derived from the various tests may be helpful (1) to the surgeon when the question arises as to the advisability of operation for the relief of arterial spasm; (2) when amputation has been decided upon, in some selected cases, the site for operation may be determined by the results of the studies; (3) in differential diagnosis of vascular disease; and (4) in early diagnosis of impaired circulation.

NOTE.—The author gratefully acknowledges the many courtesies of Dr. Thomas McCrae and of the visiting physicians to the Philadelphia General Hospital and Jewish Hospital for the privilege of observing patients on their services.

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REVIEWS.

DISEASES OF THE THYROID GLAND. By CECIL A. JOLL, M.S., B.Sc. (LOND.), F.R.C.S. (ENG.); Senior Surgeon to the Royal Free Hospital and the Miller General Hospital; Surgeon to the Cancer Hospital, etc. Pp. 682; 283 illustrations and 24 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, Cloth, $20.00.

AMONG the several monographs on this subject that have recently appeared, this one by Joll is perhaps the most comprehensive and as a reference work it probably has no equal. The preliminary chapters on the anatomy, embryology and physiology are complete in every detail. Then there are chapters on the rarer diseases of the thyroid such as acute thyroiditis, tuberculosis, syphilis, Riedel's disease, lymphadenoid and parasitic diseases. In the first part of the book are also included chapters on the parathyroids and thyroglossal cysts and tumors.

An extensive section of the book is given over to the discussion of simple goiter, which the author divides into three classes: parenchymatous, colloid and nodular. As parenchymatous goiter he considers the thyroid enlargement due to an increase in the epithelial elements of the gland without appreciable colloid accumulation. The nodular goiters are divided into those which are diffuse or multiple (adenoma) and the localized or single, in which he includes the colloid adenoma, fetal adenoma and nonparasitic cysts. These diseases are considered in detail, pointing out the symptomatology, pathology and the prophylactic as well as the active treatment.

The author gives his own classification of malignant thyroid tumors, which he treats by radical resection followed by radium or Roentgen irradiation. Thyrotoxicosis is treated more fully than any of the other diseases, and the reader is enabled to gain a picture of the disease from the time of Parry and Basedow to the present. In discussing the etiologic factors the author takes issue with Crile's theory that thyrotoxicosis is due fundamentally to disorder of the adrenals. He concludes: "It is doubtful that there is any firm basis for the theory of an adrenalin origin for exophthalmic goiter or that operations on the adrenal glands for thyrotoxicosis are justifiable." In discussing the pathogenesis of thyrotoxicosis, the neurogenic, thyrogenic, endocrine and constitutional predisposition theories are described. The symptoms and their causes are discussed in detail, giving the various technics for estimating the basal metabolic rate. There is a comprehensive chapter on the cardiovascular system in toxic goiter. Under the medical treatment, rest in bed, diet, sedatives, cardiac stimulants and iodine are discussed, as well as the dangers of the latter drug. Radiological treatment is reserved for the primary form of thyrotoxicosis associated with great restlessness and irritability and a large goiter. The surgical treatment of thyrotoxicosis is classified under three heads: intraglandular injections, ligation of thyroid arteries and thyroidectomy. The first method the author describes but does not recommend; ligation of the superior arteries however, he believes to be a useful operation. Thyroidectomy is discussed with much detail of pre-operative preparation, anesthesia and surgical technic. Complications and treatment are also fully considered.

The book is beautifully printed and illustrated, many of the anatomical and histologic plates being in color. The pen and ink illustrations of the operative technic, however, fall below the standard set by the other illustrations. Full references are given at the end of each chapter. The author's style is clear and fluent and although he mentions the work and views of other writers, he invariably expresses his own opinions based on his own wide experience. L. F.

THE ELDRIDGE REEVES JOHNSON FOUNDATION LECTURES. *Adventures in Biophysics.* By A. V. HILL, Sc.D., LL.D., M.D., F.R.S., Foulerton Research Professor of the Royal Society. Pp. 162; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Distributor: Charles C Thomas, Springfield, Ill. Price, $3.00. *The Mechanism of Nervous Action.* By E. D. ADRIAN, M.D., D.Sc., F.R.S., F.R.C.P., Foulerton Research Professor of the Royal Society. Pp. 103; 35 illustrations. Philadelphia: University of Pennsylvania Press, 1932. Price, $2.00.

THE Johnson Foundation for Research in Medical Physics was established in 1929 at the University of Pennsylvania. Its purpose is to further research in the physical aspects of the medical sciences and generally to develop the relation and application of physics to medicine. As part of these activities the Johnson Foundation Lectures were begun in 1930 as a means for presenting from time to time outstanding scientific advances in such fields of investigation. The two volumes here reviewed are based upon the first two lectures. The Director of the Foundation deserves congratulations for his choice of lectures. Professors Hill and Adrian are not only scientists of international repute—both are winners of the Nobel prize—but they have the faculty of presenting in a delightful manner subjects unfamiliar to the profession at large. Yet their subjects, belonging to the relatively new field of Biophysics, are of the utmost importance to biology in general and to medicine in particular.

Professor Hill's choice of the title "Adventures in Biophysics" is a happy one. He tells in fact of his scientific adventures, of the "real reasons why we did the things we did, the delays and imperfections and perplexities which beset us, the misery of continual failure and the joy of occasional success." It is a very human account that he thus gives of his investigations of various physiologic problems of osmotic pressure of muscle and of blood, of the state of water in tissues, of the mechanics of muscular contraction, and of other subjects.

Professor Adrian's book is as readable, and as pleasantly conversational as the preceding. He tells of the development of electrophysiology, of the action of the sense organs, of pain, of discharges in motor nerve fibers, and of the activity of nerve cells.

Both of these little books are well worth the reading; they not only tell of new advances in knowledge, but are written by men who were largely responsible for making the advances; and with all, they give a vivid account of the human side of scientific research. B. L.

ROBERT KOCH. I. TEIL 1843–1882. By BRUNO HEYMANN, A. O. Professor an der Universität zu Berlin. Grosse Männer Studien zur Biologie des Genies. Herausgegeben von Wilhelm Ostwald. Zwölfter Band. Pp. 353; illustrated. Leipzig: Akademische Verlagsgesellschaft m.b.H. 1932. Price: paper, 16 M.; cloth, 18 M.

THIS, the 12th volume of Ostwald's series of biographical studies on the biology of genius, plunges *in medias res* in a way that gives but little information about the rest of the series. Without Preface or Introduction, the story begins with a description of Koch's birthplace and his ancestors which soon leads to details of his own birth and youth. And so it runs through 330 pages that, appropriately for the year 1932, carry us to the discovery of the tubercle bacillus. The etiology of anthrax, technical bacteriologic and photomicrographic procedures, etiology of wound infections and such like furnish the bulk of the subject matter. Paper, type and illustrations are excellent, and the Reviewer wishes especially to commend the different headings at the top of each page, instead of the customary endless repetition of the titles of the book and chapter. E. K.

PAIN IN THE PLEURA, PERICARDIUM AND PERITONEUM. By JOSEPH A. CAPPS, M.D., Professor of Clinical Medicine, University of Chicago, with the collaboration of GEORGE H. COLEMAN, M.D., Assistant Professor of Medicine, Rush Medical College. A Foreword by ANTON J. CARLSON, M.D., PH.D., Chairman of the Department of Physiology, University of Chicago. Pp. 99; 33 illustrations. New York: The Macmillan Company, 1932. Price, $3.00.

THIS is a well-written book, containing a brief, concise statement of the results of "simple, direct and conclusive experiments" (Quoting from Carlson's foreword). The experiments were carried out in the following way: Trocar and cannula were inserted into the pleural, pericardial and peritoneal cavities in man; the trocar was withdrawn and a wire was inserted through the cannula; various points on the serous surfaces of these cavities were stimulated with the tip of the wire, and the location and character of the resulting pain recorded; the locations of the points of stimulation were adequately ascertained by methods described in the text. The experiments are supplemented by clinical observations in a group of cases. The authors "make no pretense to review the voluminous and somewhat confusing literature on the subject." This book is well worth reading.

F. W.

THE SIGN OF BABINSKI. By JOHN F. FULTON, Sterling Professor of Physiology in the Yale University School of Medicine, and ALLEN D. KELLER, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. Pp. 165; 65 illustrations. Springfield, Illinois: Charles C Thomas, 1932. Price, $5.00.

As indicated in the subtitle, this book goes far beyond the study of an isolated neurologic sign, important though that may be in itself, and thus should interest, as well as instruct, a correspondingly wider circle of readers. After a chapter on the known facts about the Babinski reflex—and here the historical approach is admirably supported by a photograph and a translation of Babinski's original article in the *Presse Médicale*—the author's experiments on monkeys, baboons, gibbons and 3 chimpanzees are detailed and analyzed as the basis for a theory of the evolution of cortical dominance. Incidentally they also serve as the text for a plea for the value and feasibility of using the higher primates for the experimental study of the central nervous system. . . . "In experimental neurology it is never safe to generalize from mice or marmosets to man." Also from the point of view of his convolutional markings as well as his Babinski response, the chimpanzee is shown to be nearer man than monkey—the opponents of the common ape-man ancestor notwithstanding! Four well-marked stages in the evolution of cortical control over the lower spinal centers are said to stand out from these investigations. We leave their elucidation to the reader, with the hint that careful reading will be necessary for their identification. The degree of cortical dominance has been estimated by: (1) The rate of recovery of voluntary power following a lesion of the motor area; (2) the extent of the depression of spinal reflexes thus produced, and (3) the occurrence and degree of persistence of pathologic reflexes such as the Babinski sign.

The Babinski sign is regarded as due to a lesion which withdraws corticospinal innervation of the leg, with such change in the excitability of the extensor neurones of the toes that they become "accessible" to impulses reaching the cord from the plantar surface.

The book is the excellent result of intelligent thought, skillfully applied in careful experiments and charmingly exposed by cultured writers—a combination unfortunately rare in medical literature. The contributions

of Sherrington, Cushing and McCouch to this field have been especially well appreciated. The appendices on anesthesia, surgical technique, electrosurgical methods and surgical after-care further add to the value of this praiseworthy publication. E. K.

THE EARLY DIAGNOSIS OF THE ACUTE ABDOMEN. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.), Surgeon to St. Mary's Hospital, Paddington; Senior Surgeon to the Bolingbroke Hospital, Wandsworth Common, etc. Pp. 248; 30 illustrations. Sixth edition. New York: Oxford University Press, 1932. Price, $3.25.

WE regret that such a barbarism as "the acute abdomen" should have invaded England and remained to disfigure this useful book, of which there have been 6 editions in 12 years. E. K.

ACCIDENTS, NEUROSES AND COMPENSATION. By JAMES H. HUDDLESON, M.D., Associate in Neurology, Columbia University; Attending Neurologist, Neurological Institute, New York. With a Foreword by J. RAMSAY HUNT, M.D., Sc.D., Professor of Neurology, Columbia University. Pp. 256. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

THE stated object is to present this difficult subject fairly from all viewpoints but one suspects the writer has been less frequently a claimant's witness. The chapters on Treatment and Prophylaxis are most complete though difficult of fulfillment. In the latter chapter a justified fling is taken at Mental Hygiene, where their ambitious efforts at times show too obviously a straining for effect.

A treatise covering such a difficult subject and designed for various groups of readers should be presented with the utmost clarity but here one sometimes finds an almost negroid fondness for big words:

". . . we have glanced at theories of the mind-body relationship and scrutinized more closely the functional-organic, nonstructural-structural, and psychogenic-somatogenic antitheses."

Nevertheless, the Reviewer knows of no other work giving this subject such comprehensive consideration and the embodied wealth of opinion by others is always carefully documented. N. Y.

ANATOMY OF THE HUMAN ORBIT. By S. ERNEST WHITNALL, M.A., M.D., B.CH. (OXON.), M.R.C.S., L.R.C.P. (LOND.), Professor of Anatomy, McGill University, Montreal. Pp. 467; 212 illustrations. Second edition. New York: Oxford University Press, 1932. Price, $6.25.

THE second edition of this excellent book still proves to be the best text of the anatomy of the human orbit in English. It is not only of value as a descriptive anatomy, but is also a guide to the literature of allied subjects of clinical interest. In this edition over 190 papers published since 1921 have been incorporated, the total bibliography being comprised of 650 articles. The illustrations are unusually good; many of the older illustrations now being presented in color.

This book is practically a necessity in the library of every ophthalmologist or surgeon dealing with the orbit and its contents. F. A.

INTRODUCTION TO DERMATOLOGY. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Diseases of the Skin, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., Visiting Dermatologist to the Kansas City General Hospital. Pp. 541; 183 illustrations. St. Louis: C. V. Mosby Company, 1932. Price, $5.00.

THIS comparatively small volume, as one reckons the scale of dermatologic texts, is a condensation of the massive Sutton text intended especially to supply the needs of medical students with no more than general practice in mind. The format is good, much labor and skill have been expended on intelligent condensation, and the illustrations measure up fully to the high standard heretofore set by the publishers. In spite of the condensation the literature is by no means neglected in discussion, though there is no bibliography. The index is satisfactory and as a condensed but usable compend this book is excellently representative of American practice.

J. S.

ELECTROSURGERY. By HOWARD A. KELLY, M.D., LL.D., F.A.C.S., Baltimore, and GRANT E. WARD, M.D., F.A.C.S., Baltimore. Pp. 305; 382 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $7.00.

THE authors, qualified by years of experience in this field, have compiled in one volume all the useful present-day knowledge concerning the use of the electric knife in surgery. The book contains an interesting summary of the history of electrosurgery and an elementary chapter on the physics of high-frequency currents with instructive diagrams. Then there is a chapter on the reactions of human tissues to high-frequency currents, followed by concise discussions on preparation of patients for electrosurgery, anesthesia, precautions and postoperative care. The rest of the book is devoted to a complete presentation of the application of electrosurgery in the various conditions where it has actually proved of value. Every step in the procedures recommended is clearly described in the text as well as by numerous beautiful illustrations. Those engaged in this work should find the book a great help in adding judiciously to the uses of this relatively new technique.

A. C.

MINOR SURGERY. By FREDERICK CHRISTOPHER, S.B., M.D., F.A.C.S., Assistant Professor of Surgery at the Northwestern University Medical School, Chicago. With a Foreword by ALLEN B. KANAVEL, M.D., F.A.C.S., Professor of Surgery, Northwestern University Medical School. Pp. 998; 687 illustrations. Second edition, reset. Philadelphia: W. B. Saunders Company, 1932. Price, $10.00.

THE second edition of Christopher's is an enlargement of the old. Much new material has been added, especially in the subjects of vascular diseases of the extremities, local anesthesia, bite infections, together with many new illustrations. The book has been brought up to date in most respects, but the chapter on burns still maintains the theory of toxemia as the cause of the severe symptoms.

There is no question that this work is the finest in print today covering its subject. The first edition has been found most useful not only in teaching, but also as a reference book, and the early second edition is evidence of a deserved recognition of merit.

L. F.

THE ADVANCE OF MEDICINE. By The RIGHT HONORABLE LORD MOYNIHAN, K.C.M., G.C.B., President, Royal College of Surgeons of England. Pp. 64. New York: Oxford University Press, 1932. Price, $1.00.

A GOOD survey of the progress of the art and science of medicine, with emphasis on the need for a closer alliance between physiology and the clinical branches, and further cultivation of Galenic, experimental, deductive methods as well as Hippocratic inductive observation. The surgeon, to escape "the peril of facile automatism in empty dexterities" must in future train himself thoroughly in the laboratory and in collateral research, and with the stage of perfection that the craft of surgery has now reached, must cultivate new fields of progress such as, for instance, pre-operative improvement of the tissues on which he works. This is sound advice, but little heeded in most surgical clinics. E. K.

THE SCIENCE OF SIGNS AND SYMPTOMS. By ROBERT JOHN STEWART MCDOWALL, D.Sc., M.B., F.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London, etc. Pp. 440; 6 illustrations. New York: D. Appleton & Co., 1932. Price, $7.00.

THE purpose of this book is to fill the gap in the mind of the general practitioner between his knowledge of clinical medicine and the physiologic causes of the phenomena which he observes. It attempts, with indifferent success, to review briefly both normal and abnormal physiology in relation to the more important clinical conditions. The style is often far from clear, the division of the subjects discussed sometimes poorly arranged, and the emphasis uneven. There are a few obvious misstatements of fact, and a number of the author's conclusions are open to question. Although apparently a physiologist, he does not hesitate to give therapeutic opinion and advice occasionally. The sections on the circulation, dyspnea, anoxemia and cyanosis, and the respiratory function of the blood, are perhaps the best written in the book. E. R

BOOKS RECEIVED.

NEW BOOKS.

The Mechanism of Nervous Action. The Eldridge Reeves Johnson Foundation Lecture No. 2. By E. D. ADRIAN, M.D., D.Sc., F.R.S., F.R.C.P., Foulerton Research Professor of the Royal Society. Pp. 103; 35 illustrations. Philadelphia: University of Pennsylvania Press, 1932. Price, $2.00.

The History of Dermatology. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; Sometime President of the American Dermatological Association and of the American Medical Association. Pp. 223; 33 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $3.00.

Some Factors in the Localisation of Disease in the Body. By HAROLD BURROWS, C.B.E., F.R.C.S., Assistant at the Research Institute of the Cancer Hospital (Free); Consulting Surgeon to the War Memorial Hospital, Gasport, etc. Pp. 299; 6 figures and 8 colored plates. New York: William Wood & Co., 1932. Price, $4.50.

Warner's Calendar of Medical History, 1933. New York: William R. Warner & Co., Inc.

Science and Superstition in the Eighteenth Century. A Study of the Treatment of Science in Two Encyclopedias of 1725–1750. Study No. 364 in Studies in History, Economics and Public Law. Edited by the Faculty of Political Science of Columbia University. By PHILIP SHORR, PH.D. Pp. 82. New York: Columbia University Press, 1932. Price, $1.50.

Sex and Internal Secretions. By various contributors. Edited by EDGAR ALLEN, University of Missouri. With a Foreword by ROBERT M. YERKES, Yale University. Pp. 951; illustrated. Baltimore: The Williams & Wilkins Company, 1932. Price, $10.00.

Elements of Electrocardiographic Interpretation. By LOUIS N. KATZ, A.M., M.D., Physiologist and Director of Cardiovascular Research, The Michael Reese Hospital, Chicago; Assistant Professor of Physiology, The University of Chicago, and VICTOR JOHNSON, PH.D., Instructor in Physiology, The University of Chicago. Pp. 39; 38 plates. Chicago: The University of Chicago Press, 1932. Price, $1.00.

Elektrokardiographie für die ärztliche Praxis. (Vol. 14 of Medizinische Praxis, Sammlung für ärztliche Fortbildung. Herausgegeben von L. R. Grote, A. Fromme, K. Warnekros.) By PROF. DR. ERICH BODEN, Direktor der Med. Poliklinik der Med. Akademie, Düsseldorf. Pp. 161; 91 illustrations (some colored). Leipzig: Theodor Steinkopff, 1932. Price, Paper, Rm. 12; Cloth, Rm. 13.50.

Abstracts of Publications Nos. 17 to 21 of The Committee on the Costs of Medical Care. *Surveys of Organized Medical Service.* Abstracts of Five Reports on Organized Facilities for the Provision of Medical Care. Pp. 67. Washington, D. C.: The Committee on the Costs of Medical Care, 1932.

Chapters in American Obstetrics. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University School of Medicine. Pp. 90; 10 plate illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $2.00.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Fifth Session. By PROF. DR. BRUNO KISCH, KÖLN. Pp. 362; 95 illustrations and 1 table. Leipzig: Theodor Steinkopff, 1932. Price, Paper, Rm. 20.

Following the custom established in earlier volumes, whose main themes were the heart, vessels, blood, and digitalis, this volume is particularly concerned with blood pressure and the peripheral circulation. An excellent survey of German progress in recent years in these fields is afforded by the four chief referate and forty odd other articles.

A Text Book of Midwifery in the Tropics. By V. B. GREEN-ARMYTAGE, M.D., F.R.C.P. (LOND.), F.C.O.G., LT.-COL. I.M.S., Chevalier of the Legion of Honor, etc., and P. C. DUTTA, M.B., F.R.C.S., D.G.O., Captain, I.M.S. Pp. 306. Calcutta: The Book Company., Ltd., 1933. Price, Rs. 5/–.

Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System. By HARVEY CUSHING, Professor of Surgery (Emeritus), Harvard University, and Recently Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 234; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $5.00.

A Suggestion for an Experimental Attempt at Local Immunization in Poliomyelitis Through Irradiation of the Portals of Entry. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 15. Cleveland: Mount Printing Company, 1932.

Autogenous Vaccination Through Irradiation. Immunization Through the Photochemical Release of Antigen from Infected Tissues. By S. PESKIND, B.S., M.D. Pp. 17. Cleveland: Mount Printing Company, 1932.

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PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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A Coagulo-flocculation Test for Malignant Tumors. — A method whereby malignancy might readily be diagnosed is, of course, one of the great desiderata in medicine. The reasons are too obvious to need to be mentioned. One of the grounds of attack of this problem which has been extensively investigated is a complement-fixation test with the blood serum of a patient presumably ill with a malignant tumor. WEISS (*Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 127) reports on a diagnostic procedure for malignant tumors which depends upon a coagulo-flocculation reaction when the blood serum inactivated at 55° C. is added to an antigen of finely ground beef heart extracted with 95 per cent alcohol and in turn diluted with 0.5 per cent water solution of sodium sulphate. The detail of the test will not be reported. Suffice it to say that it can be carried out apparently with greater ease than an ordinary Wassermann. In regard to the results, the author states that in 179 malignant tumors, 85 per cent of the reactions were positive, while in 154 cases of various diseases and 105 cases of benign tumors, nonspecific reactions occurred in approximately 2 per cent of the cases. In this brief report no data are given concerning the age of the malignant tumors. It is to be hoped that diagnosis by this method may be obtained with early malignancy as well as with large, far advanced growths which the tyro can diagnose.

Lipolytic Activity of Rat Tissues in Experimental Leprosy.—One of the suppositions to explain whereby a possible therapeutic action is obtained with chaulmoogra oil in leprosy, is that this oil may stimulate the nonspecific lipolytic activities of the tissues enabling them to attack the fatty acid capsules of Bacillus lepræ. EMERSON, ANDERSON and LEAKE (*Soc. Exp. Biol. and Med.*, 1932, **30**, 150) undertook a study of the lipolytic activity of leprous tissue in experimental rat leprosy. They report, in the study, on the destruction of lipoids in the tissues in the presence of leprosy as compared with that in the normal animal. They found that leprous tissue is more significantly lowered in lipolytic

activity than other tissues in either the infected or normal rat; that the leprous tissue is remarkably constant in lipolytic action compared with other tissues, and that the presence of severe leprous lesions lowered the lipolytic activity of most of the tissues in the body.

SURGERY

UNDER THE CHARGE OF

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Postoperative Pulmonary Complications.—Ever since the introduction of ether as an anesthetic agent, respiratory complications after anesthesia and operation have added to the morbidity and mortality of surgical procedures. For many years the more severe of these complications were known as "ether pneumonia." With the advent of each new anesthetic, claims were made that the incidence of respiratory complications would be reduced after its use. Unfortunately the claims too often proved to be untrue. Complications were often as frequent after local anesthesia as after general anesthesia.

In 1920, CUTLER and HUNT (*Arch. Surg.*, 1920, **1**, 114) suggested that minor pulmonary infarction could account for a large number of the postoperative respiratory complications. Shortly after this the attention of surgeons was called to a hitherto rarely recognized lesion, which has since become known as pulmonary atelectasis (LEOPOLD, AM. J. MED. SCI., 1924, **167**, 421). Surely embolism could not account for this complication, and with increasing care in the examination of patients with respiratory complications after operation, the incidence of atelectasis has increased.

Within the past several months two articles have been published which reëmphasize the incidence, morbidity and mortality of these troublesome complications (ELIASON and MCLAUGHLIN, *Surg., Gynec. and Obst.*, 1932, **55**, 716; KING, *Ibid.*, 1933, **56**, 43). In the former study there were 120 cases with postoperative pulmonary complications in a series of 7326 operations, a morbidity of 1.68 per cent. Of the 120 cases 32.5 per cent died, which account for 15.5 per cent of their total operative mortality. The yearly variation of the complications was no greater than would be expected in this type of statistical data. The incidence of these complications in the earlier and later papers, except that of King, has been remarkably constant, 2.5 to 3.5 per cent (WHIPPLE, *Surg., Gynec. and Obst.*, 1917, **25**, 621; ELWYN, *J. Am. Med. Assn.*, 1924, **82**, 389). Bronchopneumonia was the complication in about one-third of the cases while atelectasis was the complication in less than one-sixth of the Eliason and McLaughlin series. Only 18 cases

of lobar pneumonia were encountered, while in 9 pulmonary embolism was the cause of the complication.

Similar to the findings of FEATHERSTONE (*Brit. J. Surg.*, 1925, **12**, 487) and RAVDIN and KERN (*Arch. Surg.*, 1926, **13**, 120) there were more postoperative pulmonary complications during the winter months when upper respiratory disease is more common in the community.

There is apparently no definite relationship between these complications and the anesthetic agent. The experience in the Hospital of the University of Pennsylvania, from which Eliason and McLaughlin collected their data from all the General Surgical Services, is that local and spinal anesthesia are associated with postoperative pulmonary complications just as frequently as are ether or nitrous oxid and oxygen. MCKITTRICK, MCCLURE and SWEET (*Surg., Gynec. and Obst.*, 1931, **52**, 898) have shown that with spinal anesthesia there has been an increase in the postoperative pulmonary complications when compared with ether. Foss and KUPP (*Surg., Gynec. and Obst.*, 1930, **51**, 798) had just as many pulmonary complications after spinal anesthesia as with inhalation anesthesia. Eliason and McLaughlin believe that there is a definite correlation between the incidence of the complications and the duration of the anesthetic, although this point is still debatable. It may be that the longer period of anesthesia was required for operations which are known to be more frequently associated with postoperative pulmonary complications.

In KING'S (*Surg., Gynec. and Obst.*, 1933, **56**, 43) series there were 7065 operations with 426 pulmonary complications, a morbidity of 6 per cent and a mortality of 22.5 per cent in those patients who developed such complications. However, of the patients that died after a respiratory complication, the complication was the contributing cause of death in only 37, an actual mortality due to the respiratory lesion of 8.2 per cent of the respiratory morbidity. Thus, while the morbidity in King's series is higher than is that found in Eliason and McLaughlin's series, the mortality of the morbidity is considerably lower. This would seem to indicate that many of King's cases were of a much milder nature than those considered in the data of Eliason and McLaughlin. If one considers only the severe cases which King reports, his figure for the morbidity would be 0.73 per cent, which is even somewhat lower than that of Eliason and McLaughlin. In King's data the respiratory complication was the cause of, or the major contributing cause of death in 0.52 per cent of the 7065 cases; while in the 7326 cases of Eliason and McLaughlin the mortality in cases with pulmonary complication in the whole series was 0.54 per cent. Both papers report a higher incidence in men than in women, but King found no seasonal variation of the complications. In both series high abdominal operations were accompanied by a higher incidence of complications than operations on any other site.

CHURCHILL and MCNEILL (*Surg., Gynec. and Obst.*, 1927, **44**, 483), HEAD (*Boston Med. and Surg. J.*, 1927, **197**, 83) and POWERS (*Arch. Surg.*, 1928, **17**, 304) have found that following upper abdominal operations the vital capacity was reduced 50 to 88 per cent of the pre-operative level, while in lower abdominal operations it was reduced 20 to 70 per cent. OVERHOLT (*Arch. Surg.*, 1930, **21**, 1282) found that a disturbance of the normal subatmospheric pressure in the peritoneal

cavity, as results after the entrance of air, causes a restriction of diaphragmatic activity, and MULLER, OVERHOLT and PENDERGRASS (*Arch. Surg.*, 1929, **19**, 1322), SISE, MASON and BOGAN (*Anesth. and Analg.*, 1928, **7**, 187) and PATEY (*Brit. J. Surg.*, 1930, **17**, 487) have shown that following an abdominal operation there is a diminished excursion of the diaphragm, which results in diminished pulmonary ventilation. The lowered vital capacity is probably also in large part due to a splinting of the abdominal musculature because of pain and the unwillingness of the patient to breath normally, together with the change in the intraperitoneal pressure, which is associated with an abdominal exploration. Certainly the last word has not been said on the perennial subject of postoperative pulmonary complications.

THERAPEUTICS

UNDER THE CHARGE OF

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The Danger of Peripheral Nerve Injuries from Intravenous Injection and Its Avoidance.—Following the careful observation of 5 instances of serious and lasting injury to the median nerve or to the lateral or medial cutaneous antebrachial nerves from intravenous injection of calcium preparations, ZUTT (*Deutsch. med. Wchnschr.*, 1932, **58**, 1321) feels that, although the frequency of nerve injury is comparatively small, the effects are of sufficient importance to justify every effort for its avoidance. The author directs attention to the topographic anatomy of the veins and nerves lying in the elbow region and points out that the median vein which connects the cephalic and the basilic veins at the elbow is the only available one which is not accompanied by nerves or which does not overlie a nerve. Nerve damage can with certainty be avoided only if intravenous injections be made into this median vein. The author points out, however, that owing to anatomic variations, to subcutaneous fat and to the state of laxity of the subcutaneous tissues, it is not always possible to utilize this vein. Where such is not the case intravenous injections should always be made into the cephalic vein because in the event of perivenous escape of solution the only nerve which might be damaged is the lateral antebrachial sensory nerve. If, however, injection be made into the basilic vein, it is impossible to avoid the danger of damaging either the corresponding medial sensory nerve or the underlying median nerve or both of these nerves. The author points out the interesting fact that every instance of nerve damage from intravenous injections which has come to his personal attention was associated with the injection of a salt of calcium and he suggests, therefore, that especial care be observed where this drug is employed.

Intravenous Vaccine Therapy in Chronic Arthritis.—Clawson and Weatherby (*Ann. Int. Med.*, 1932, **5**, 1447) report the results obtained by others as well as by themselves indicating, if not establishing, the close relation between chronic arthritis and streptococcal infection. They also present the results of a series of animal investigations which show that subcutaneous administration of vaccine produces relatively little increase in immunity as measured by the agglutination titer and by local tissue response to the subcutaneous injection of living streptococci. At the same time subcutaneous administration of vaccine not only fails to desensitize but actually promotes hypersensitiveness or allergy. They further establish the fact that nonspecific vaccine therapy is detrimental rather than beneficial in animals. In contrast to these findings experiments indicate that the intravenous administration of streptococcus vaccine produces a very high degree of immunity combined with an effective desensitization. It is also demonstrated that the immunity is species specific for streptococci but not type specific. On the basis of these experimental results the authors treated a group of 300 patients suffering from chronic infective arthritis by weekly intravenous injections of streptococcus vaccine made from a culture obtained from a case of acute rheumatic fever and which was of low virulence because of its continued growth for 9 years. The initial dose employed was 100,000,000 organisms which was increased by 100,000,000 at each subsequent injection. Only slight reactions occurred and in only about half of the patients. The reaction seemed to be unrelated to clinical improvement. It was rarely necessary to administer more than 8 to 10 injections. Definite clinical improvement occurred in 74 per cent of the patients, questionable improvement in 6 per cent and no improvement was observed in about 16 per cent. The authors feel that this method is based upon sound experimental investigation and that the clinical results are sufficiently good to justify further employment of the method for treatment in man.

PEDIATRICS

UNDER THE CHARGE OF

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The Treatment of Coughs With Suprarenal; Whooping Cough.—Barbour (*Arch. Pediat.*, 1932, **49**, 816) says that the many remedies which have been offered for the treatment of pertussis differ in name more than in action. None of them has produced any decline in the incidence, morbidity and mortality of the disease. Each of these remedies may be roughly classified in one of the following categories: sedatives, antispasmodics or nonspecific proteins. The effect of the sedatives and antispasmodics is probably mainly one of symptomatic relief. Although the pertussis vaccines may have some specific antitoxin effect, the results may be attributed largely to nonspecific protein reactions. There is no consistent dependence on any one, or any com-

bination of the various remedies to give a prompt and a continued relief. Over a period of 18 months suprarenal, or thyroid and suprarenal and a nonspecific protein was administered to 85 cases. The results of the treatment were as follows: In 50 per cent (44 cases) there was a striking improvement of the symptoms within 1 to 2 days and a complete disappearance of the cough within from 1 to 4 weeks following the use of the suprarenal. In 20 per cent (14 cases) a prompt and increasing relief followed the administration of the thyroid and suprarenal. A complete cure followed within from 1 to 4 weeks. The condition of 25 per cent (23 cases) responded very well to the combined endocrine and protein treatment, with a complete disappearance of the cough in from 2 to 4 weeks. In 4 cases (5 per cent) the treatment seemed to have little or no effect. In none of the cases was there any complications or sequelæ.

Immunization Against Measles by Placental Blood.—De Souza (*Arch. de méd. d. enfants*, 1932, **35**, 633) during a period of 4 years injected 160 children who had been exposed to measles, with blood taken from the human placenta. The number of cases in which immunization was obtained varied between 85 per cent in the first year of the observation and 63.4 per cent in the fourth year. In those cases in which immunization failed, the measles almost always occurred in an attenuated form, generally without catarrh of mucous membranes and of the bronchi. The death rate among the patients who contracted measles in spite of the injection was only 2.27 per cent, as compared to 12.7 per cent among the noninjected patients. It is suggested that the drop in the percentage of immunizations in the fourth year was due to tyndallization of the placental blood with formaldehyde solution. This procedure was resorted to in the fourth year because of the persistence of occasional suppurations, but a much smaller percentage of immunizations were obtained with 10 cc. injections of blood so treated than with the 4 cc. injections of nontyndallized blood or of blood tyndallized without formaldehyde solution, which were given in the first 3 years. After the blood has been collected from the placenta under strict aseptic conditions and has been sealed immediately in sterile ampules, it is necessary only to tyndallize without formaldehyde solution once or twice at from 52° to 54° C. to be ready for use. The injection is usually followed by a rise of temperature which usually lasts for 2 days. The injection should be given intramuscularly and care should be taken to avoid leakage into the subcutaneous tissue. The author believes that the immunity to measles produced by placental blood is due to the individuality of this blood. With its amino acids and other hypothetic products of internal secretion, it probably acts as a nonspecific antigen, stimulating the production of antibodies and resulting in a group immunization to anaphylactic and antiphylactoid states.

Cyanosis in the Newborn.—Hunt (*Am. J. Dis. Child.*, 1932, **44**, 1268) analyzed the results obtained in 118 postmortem examinations in an attempt to determine the more common pathologic lesions causing cyanosis in the newborn. It is realized that the causes of death and of cyanosis are not synonymous, and that several facts may be involved. Hemorrhage, whether intracranial, pulmonary or intraäbdominal, can-

not be disregarded as a contributing cause in many instances. Intracranial lesions, although frequently found at postmortem examinations, are not always of sufficient severity to produce symptoms. This is true especially of small tentorial tears, which must be disregarded usually. On the other hand, extensive unilateral or bilateral tears of the tentorium accompanied, as they most frequently are, by profuse hemorrhage, would seem sufficient cause for cyanosis. Meningeal bleeding may occur in the absence of tentorial lesions, and is often profusely distributed over the cerebral hemispheres or at the base. These two types of lesions are usually the direct result of birth trauma, and consequently cyanosis will appear in the first few days of life. The cyanosis accompanying congenital heart disease is due to the mixture of venous with arterial blood or to stasis. With such abnormalities, the blueness varies directly with the activity of the infant, and does not appear until several weeks after birth. Unless the lesion is severe, life is possible, and in some cases the child survives for some years. The relatively few cases that were studied in this series are not indicative of the true frequency of cyanosis as a manifestation of congenital cardiac abnormalities. Pneumonia is the most common single lesion found in these infants. The disease does not differ from that seen in older children, except for the variability of the signs. The appearance of a hyalin membrane, which is probably the result of aspirated amniotic fluid, is more common than was believed formerly. In small amounts, this is of little significance. In the cases in which it forms a membrane lining the alveoli of large sections of the lung, it cannot but cause respiratory embarrassment. Persistent cyanosis appears early in the life of these infants, and this may be the only sign present. Other pathologic conditions may produce cyanosis in the newborn, but they are relatively infrequent. The greatest difficulty in diagnosis is usually between pulmonary and cerebral lesions. Lumbar puncture or roentgenologic examination of the chest may be of assistance in establishing the cause of cyanosis, but at times these procedures may give no aid. In the infants coming to postmortem examination, intracranial lesions, including hemorrhage and tentorial tears are the most frequent causes of cyanosis, but as a single severe entity pneumonia is the prominent factor.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Vaginal Wounds Due to Intercourse.—The German literature frequently contains reports of serious vaginal wounds as the result of sexual relations, and in reporting a case of this kind Sztehlo (*Zentralbl.*

F. Gynec., 1932, **56**, 2121) states that the etiology is not always the same, since in some cases it is dependent on abnormal positions during intercourse, such as knee-elbow position, unusual size of the penis and developmental anomalies of the female genital organs. The case he reports is that of a poorly developed girl, aged 20 years, who presented a tear in the right vaginal vault large enough to admit three fingers. This injury followed a normal intercourse and the hemorrhage was so severe that the hemoglobin dropped to 40 per cent. The laceration extended about 1 inch into the parametrium. The spurting bloodvessels were ligated and the wound was sutured with considerable difficulty as the sutures tended to tear out. Following suture the vagina was packed for 24 hours. It is interesting that the large majority of such vaginal injuries occur on the right side, as in this case, and he believes that this selection is due to some anatomic reason. Since the rupture in this case followed intercourse in the normal position it was probably due to hypoplasia of the vaginal wall, especially since the vagina was so friable when suture was attempted and the girl was generally poorly developed. In a collected series of Neugebauer there were 22 deaths among 157 cases, the mortality being due to hemorrhage, sepsis and peritonititis. The treatment of such injuries consists primarily of arresting hemorrhage. If the wound is recent and uncontaminated, suture of the edges suffices, but in wounds of longer duration, after controlling hemorrhage, drainage should be instituted for a few days.

Uterine Allergy.—In stating that uterine symptoms may be due to food allergy, ROWE (*Am. J. Obst. and Gynec.*, 1932, **24**, 333) has given the gynecologists something to think about. The abundance of smooth muscle and of mucous membrane in the tubes, uterus and vagina emphasizes the probability that allergic reactions may occur in this tract even as they do in the bronchial or gastrointestinal tracts. He believes that painful, irregular, scanty or profuse menstruation may be due to food allergy. Such disturbances may be associated with severe nausea, vomiting, acidosis, migraine, headaches or other allergic disturbances. Careful study of the patient with physical and laboratory examinations must be made so that all existing pathology is discovered. Gynecologic lesions of all types must be ruled out in patients suspected of allergy, but it should be remembered that allergic reactions may accompany other disease pictures. Skin tests with all foods and preferably with other types of allergens should be carried out. Elimination diets modified by skin reactions to foods, as well as by a history of specific food idiosyncrasies, should be prescribed. By the gradual development of such diets the allergy-producing foods can be discovered. Other conditions aside from abnormal uterine bleeding, which he believes may sometimes be of allergic nature, include leukorrhea, edema of the tubes, vagina or labia and excoriation of the labia and of the surrounding skin.

Menorrhagia Due to Blood Dyscrasias.—The occurrence of menorrhagia is so frequently due to some lesion of the female generative organs that blood dyscrasias are not often considered as causative factors. KAHN (*J. Am. Med. Assn.*, 1932, **99**, 1563) studied 45 cases of blood disease in women during the reproductive period, and found that a normal menstrual flow was present in 51 per cent, there was

excessive flow in 33 per cent, while in 15 per cent it was diminished. The menstrual deviation figured prominently in the symptom complexes which brought these patients to their physicians. He believes that sufficient emphasis has not been placed on disturbance of the menstrual flow occurring in those cases in which no pelvic abnormality is present. In some cases curettage has been performed, but the bleeding soon recurs. In such cases a complete study of the blood will sometimes reveal an underlying blood disease as the etiologic factor, the menstrual disturbance being but a local manifestation of a systemic disorder.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Eclampsia With Amaurosis Due to Detachment of the Retinæ.—CROWTHER and HAMILTON (*Med. J. Australia*, 1932, **2**, 177) report bilateral detachment of the retina occurring in a primipara, aged 23 years, who developed eclampsia in the seventh month of pregnancy. On the date of her admission to the hospital, marked generalized edema was present, the systolic blood pressure was 200 and the urine contained large amounts of albumin. Blurring of vision commenced the next day and progressively increased to almost total amaurosis in 8 days. The patient was delivered on the seventh day and had an eclamptic convulsion shortly afterward. Her condition improved rapidly after delivery. She left the hospital in 3 weeks and showed no evidences of residual chronic nephritis. Marked generalized edema of the retina with detachment of the lower and temporal portions was present in each eye when the patient was first examined 1 day after delivery. Reattachment of the retina was complete in 3 weeks. Residual pigment changes were striking. Vision had improved in 1 month to 6/36 right and 6/24 left, with proper refractive correction. Hamilton thinks that the edema of the retina was a part of the generalized edema of the body tissues. The dark color of the detachment in its acute stage and the residual pigment changes suggest that the source of origin of the edema was the choriocapillaris, so that the detachment involved both the retina proper and the retinal pigment epithelium.

Association of Sclerosis of the Cerebral Basal Vessels With Optic Atrophy and Cupping.—KNAPP (*Arch. Ophth.*, 1932, **8**, 637) reports 10 cases of optic atrophy with excavation of the disks simulating that of glaucoma, but without elevation of the intraocular tension. Such cases have usually been considered as atypical glaucoma, the optic atrophy and excavation having been caused by a previous rise of tension,

by inherent weakness of the lamina cribrosa, or by a solution of the nerve fibers by an abnormal action of the intraocular fluid as it passes through the optic nerve. The field changes in these 10 cases were different from those usually seen in glaucoma. There was a tendency to altitudinal defects and the blind spot changes were not characteristic. The progress of the loss of vision was very slow. An operation for the reduction of tension was performed in 2 of the cases without any effect on the course of the disease. The patients in this series showed general symptoms of a moderate general arteriosclerosis without particular cerebral manifestations. Their ages varied from 53 to 75 years. Stereoscopic roentgenograms of the head revealed in all cases calcification of the internal carotid, posterior communicating, or ophthalmic arteries. The author believes, therefore, that the optic atrophy in these cases is of descending type, due either to direct pressure of sclerosed basal vessels on the optic nerves anterior to the chiasm, or to the development of areas of softening in the nerves from closure of nutrient bloodvessels.

The Prognosis of Albuminuric (Angiospastic) Retinitis.—HEIDER and LÜRMANN (*Münch. med. Wchnschr.*, 1932, **79**, 1585) believe that the retinitis which occurs in chronic nephritis and that in malignant nephrosclerosis (malignant hypertension) are of the same type and have the same ophthalmoscopic appearances and the same pathogenesis (angiospasm). In general they have also the same serious prognosis. Healing or improvement of the retinitis and improvement of the systemic condition occur in a certain number of cases, especially in acute nephritis and eclampsia. In chronic nephritis and in malignant nephrosclerosis, as a rule, any resorption of the retinitis is only temporary and fresh lesions recur until the time of death. The occurrence of angiospastic retinitis in primary hypertension without renal insufficiency indicates the approach of renal failure which may, however, be postponed for several years. The occurrence of arteriosclerotic retinitis does not have the same significance. In patients with malignant nephrosclerosis with manifest renal insufficiency and retinitis the outlook is uniformly hopeless. The development of angiospastic retinitis is a similarly ominous sign in chronic nephritis. However, an edematous retinitis which develops coincident with a state of pseudouremia in a chronic nephritis in the stage of renal insufficiency, or in a malignant nephrosclerosis, will subside rapidly under proper management of the systemic condition, and the patient may live comfortably for several years without recurrence of the retinitis. The authors believe that both the cerebral manifestations of the pseudouremia and the retinitis are due to edema consequent upon arterial ischemia of the brain and retina. With the relief of the arterial constriction the edema subsides, the cerebral manifestations and the retinitis disappear, and the patient returns to his former status. This improvement is usually associated with a drop in blood pressure. If retinitis develops in malignant nephrosclerosis without associated pseudouremia, though temporary regression of the retinitis may occur either through a lowering of the blood pressure or through improvement in the strength of the heart, there will be no permanent alteration of the patient's condition or of the ultimate prognosis.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Relation of the Histopathology of Nasopharyngeal Neoplasms to Their Radiosensitivity.—To Kocher, once said Pirogoff, "The most perfect satisfaction which one can have in medicine comes through the thorough study of one special chapter in every direction and from every point of view. , . ." And so, beginning with the clinical observation that some pharyngeal neoplasms responded much more readily to radium therapy than others, the oncologist—by subjecting his problem to virtually every available form of investigation—not only has told us why, but also has shown us how fruitfully to apply this knowledge to human needs. Not untimely, therefore, BECK and GUTTMAN (*Ann. Otol., Rhinol. and Laryngol.*, 1932, **41**, 349) recount the circumstances which have led up to the recognition of the three commonly encountered neoplasms arising from epithelial structures of the oropharynx and nasopharynx. Histopathologically, these three malignant tumors are called: (1) Squamous-cell carcinoma; (2) transitional-cell carcinoma, and (3) lymphepithelioma. Each of these neoplasms presents an individually characteristic microscopic picture. Clinically, too, the transitional-cell carcinoma and the lymphepithelioma behave similarly—in that, though small (often grossly undetectable), they metastasize early to cervical lymph nodes, and their anaplastic cells are precociously sensitive to radium. Contrariwise, the squamous-cell carcinoma usually can be found without difficulty, grows slowly, invades regional lymphatics relatively late, and the well differentiated cells are notoriously "radio-resistant." It follows, then, that at the present time surgery offers most for the well-known squamous-cell types, and radium for the other two; that here, as always, efficient treatment depends upon correct diagnosis; but that if, for any reason, the histopathologic diagnosis is unavoidable or doubtful, the imperativeness of prompt action justifies the employment of a "therapeutic test"—which in this case is radium.

Ten Commandments for Sinus Sufferers.—The more expediently to manage their cases, MANDELBAUM (*Laryngoscope*, 1932, **42**, 710) issues to his patients with paranasal sinusitis certain data designed to facilitate recovery and to prevent recurrences. Briefly, these admonitions, or "commandments," may be set forth as follows:

1. Do not wet your hair on leaving your home in the morning, particularly in cold weather.
2. Do not swim or dive.
3. Do not get wet feet.
4. Do not smoke or "drink" during acute attacks.
5. Do not go without a hat except in the midsummer months, and not even then too long in the very hot sun.

6. Do not stay in a draught either while asleep or awake.
7. Do not overindulge in food.
8. Do not take cold shower baths in the morning, particularly in cold weather, unless donning a rubber cap. If you must do so, do not leave the house before your body is warm. Better still, bathe before retiring.
9. Do not wear summer underwear in the late fall, winter or early spring.
10. Do not neglect your general health.

RADIOLOGY

UNDER THE CHARGE OF

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A Critique of the Roentgen Signs of Infantile Scurvy.—After enumerating the accepted roentgenologic signs of infantile scurvy KATO (*Radiology*, 1932, **18**, 1096) holds that there is but one conclusion to draw, namely, that the majority of these signs are not pathognomonic. The continued use of such terms as the "Trummerfeldzone" and "Wimberger's sign" as diagnostic of infantile scurvy leads to confusion. Pelkan's triad in the diagnosis of latent scurvy is a valuable adjunct, but it is not absolutely characteristic. Beading of the ribs is common both in infantile scurvy and rickets. Separation of epiphyses is found most frequently in infantile scurvy, but it may also occur in other conditions. The white line of Fraenkel is the least characteristic of scurvy for it is merely a phenomenon of hypercalcification at the end of a long bone, which is seen in many diverse pathologic conditions. The one sign which is absolutely unique in infantile scurvy is that of subperiosteal hemorrhage during the third stage of the disease. This can only be inferred clinically, and the final diagnosis must rest on the roentgenologic evidence. The author insists that these criticisms do not constitute an attempt to minimize the diagnostic value of the Roentgen evidence, but he desires to emphasize the necessity of broadening the experience of both clinicians and roentgenologists in evaluating and interpreting the roentgenologic signs of infantile scurvy.

Evaluation of Pneumoventriculography and Encephalography.—ADSON (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 657) presents a critical tabulated review of 217 cases of tumor or suspected tumor of the brain of which 187 were operated on or explored. Careful neurologic examination, with the aid of ordinary roentgenograms and ophthalmologic examination permitted localization of 69 per cent of the tumors. Ventriculography gave positive localizing evidence in 25 per cent of the cases not localized clinically. Ventriculography is of par-

ticular value when the patient is comatose and when, therefore, it is difficult to elicit neurologic signs. It is valuable in distinguishing between tumors of the frontal lobe and of the cerebellum and in the localization of basoarachnoiditis obstructing the 4th ventricle. Occasionally it may be resorted to in cases of chronic brain abscess, but it would be unwise to employ it as a routine. Encephalography is of greatest value in the differential diagnosis and localization of arachnoiditis, posttraumatic lesions and atrophy of the brain. It is an unsafe procedure in the presence of increased intracranial pressure. The author is of the impression that encephalography is being abused since the clinical features are often sufficient to make possible the diagnosis without subjecting the patient to the distressing symptoms which attend encephalography.

Spectrophotometric Analysis of the Color of the Skin Following Irradiation by Roentgen Rays.—From their investigations, HARRIS, LEDDY and SHEARD (*Radiology*, 1932, **19**, 293) conclude that spectrophotometry offers an accurate method of recording changes in color of the skin following irradiation. The course of the erythema is cyclic over a period of months with fairly definite points at which the erythema is at a minimum. The pigment is immediately affected by irradiation and follows a course independent of that of the erythema; so that the hue of the skin remains constant.

Treatment of Giant-cell Bone Tumors by Roentgen Irradiation.—During a period 25 years 26 cases of giant-cell bone tumor were treated by PFAHLER and PARRY (*Am. J. Roent. and Rad. Therap.*, 1932, **28**, 167). The first case is believed to be the earliest case on record and was originally considered to be osteosarcoma. All cases have shown a definite and satisfactory response to Roentgen therapy, more satisfactory in the young than in the old. The authors favor fractional doses with rays of high voltage. The damage to epiphyses was observed. They believe that irradiation is definitely superior to surgery in treating these tumors, and they hold that curetting or crushing the bone is not of advantage.

Roentgen Ray Therapy in Dermatology.—It is held by FOX (*Arch. Phys. Ther., X-ray, Rad.*, 1932, **13**, 550) that roentgenotherapy is used too frequently and in too large doses, especially to the exclusion of other therapeutic measures, for skin diseases. A large number of superficial inflammatory dermatoses can be cured without Roentgen rays, and a still larger number can be cured with only small amounts of radiation. In fact, Roentgen rays alone produce permanent cures in a relatively small number of skin diseases. Employment of the Roentgen rays is indicated primarily in localized or infiltrating dermatoses. A generalized or universal dermatosis is by itself a contraindication for the use of Roentgen rays except for very small doses judiciously administered.

Visceral Displacement in Pneumonia.—Among 40 consecutive cases of lobar pneumonia observed by C. WU (*Radiology*, 1932, **19**, 215) 5 showed displacement of the heart and trachea toward the affected side, and 22 showed elevation of the diaphragm on the affected side. Both dis-

placements were noted only on full inspiration. Displacement begins early, sometimes before it is possible to demonstrate consolidation, persists usually throughout the course of the disease, and may continue for a time after resolution has occurred. Mediastinal displacement occurs more often in children; elevation of the diaphragm more often in adults. Roentgenologic demonstration of either displacement may be important in distinguishing pneumonia from pleural effusion or other disease.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Nonspecific Therapy in Mental Disorders.—GRAVES (*Lancet*, 1932, **9**, 57), in 1922, suggested that in mental disorders injections of colloidal calcium oleate caused or increased a reaction in or around septic foci with a resulting reduction of general toxemia and improvement of nutrition, circulation and mental state. Other agents which have been widely used here are colloidal sulphur in oily or watery suspension and TAB vaccine. The focal effects of an infection consist of an active stage, appearing within 24 hours as an area of increased vascularity, pain, swelling, exudation and disturbance of function in or around any localized lesion, and a stage of resolution during which there is a progressive decrease in the inflammatory reaction until the *status quo ante* is reached or passed. If the sepsis is open the focal reaction may be enough to cause a discharge or a reduction of the persistent infection with the consequent cessation of mitigation of the toxemia and mental recovery. When the sepsis is closed, however, nonspecific therapy is not likely to bring about recovery especially if the focus contains necrotic material. The result is more likely to be increased toxic absorption, greater toxemia and exacerbation of symptoms.

Viewpoints on Stuttering.—BROWN (*Am. J. Orthopsych.*, 1932, **2**, 1) gives a brief symposium on the theories and practices which are widely employed in attempting to understand, to treat and to prevent stuttering. On the basis of certain facts and principles which are common to most of these theories and practices, an attempt is made to formulate a reasonable hypothesis upon which both therapeutic and prophylactic work may be based. The following procedures are suggested as the basis of a rational method of attempting to solve the problem of stuttering which, to be more exact, is the personality problem of the stutterer: (1) The study of each stutterer as an individual personality, striving and failing to adjust himself adequately to social situations through

speech. (2) The application of accepted principles of physical and mental hygiene for the purpose of integrating the stutterer's personality and enabling him to make adequate adjustments to social situations. (3) The instruction of teachers, parents and others in the nature of these principles and the training of these persons in applying them, not only as a means of treatment but as a means of preventing stuttering. (4) The conducting of research into the cause, origin and nature of stuttering for the purpose of developing, if possible, more adequate therapeutic and prophylactic techniques.

Psychosis: Its Importance as a Presenting Symptom of Brain Tumor.—ADELSTEIN and CARTER (*Am. J. Psychiat.*, 1932, **12**, 317) state that the incidence of brain tumor as a clinical entity is about 1 per cent. The psychosis may be the first presenting symptom. They feel that all cases presenting a psychosis should receive a thorough neurologic examination to rule out a possible organic basis. Visual and auditory hallucinations are of localizing value only if distinct and apart from the psychosis. The mental phenomena in brain tumor may be regarded as focal in nature only if the neurologic examination will bear out the localization. The cases studied, the authors feel, bear out the contention of Gordon Holmes that "lesions of the frontal lobe produce mental symptoms perhaps more frequently than those of any other part of the brain except the corpus callosum."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Bacteriophage Therapy.—It is often difficult to evaluate methods of treatment in man because of the many uncontrollable factors involved. The use of animals which are subject to certain infections offers better opportunities for obtaining more reliable results. The early optimism as to the therapeutic value of bacteriophage has been succeeded by a feeling of uncertainty. COLVIN (*J. Infect. Dis.*, 1932, **51**, 17) reports from the Department of Immunology, Yale University School of Medicine, that with streptococcus lymphadenitis of guinea-pigs he was unable to find any curative value in a bacteriophage which showed maximum virulence *in vitro* against the etiologic organism. He believed that within the tissues the conditions are such as to inhibit the action of a bacteriophage that is thoroughly effective *in vitro*, and from a review of the results of bacteriophage therapy in natural and experimental diseases of laboratory animals it appeared to him that there had been no real therapeutic successes since the early experiments of d'Herelle with fowl typhoid.

Lymph Pressures in Sterile Inflammation.—FIELD, DRINKER and WHITE (*J. Exp. Med.*, 1932, **56**, 363) report observations on lymph pressure in the leg lymphatic of dogs. Sterile inflammation was produced by immersing foot in hot water. A column of lymph was established by cannulating one or both of the two main lymphatics at the ankle of the hind leg and attaching to a vertical manometer through a Y tube. In one series of experiments, the foot was placed in water at 100° C. for 2 minutes. An advanced degree of inflammation resulted, with the production of lymph pressures ranging from 78 to 120 cm. of lymph. This pressure, closely following the venous pressure, rose immediately upon immersion, reaching a maximum in 3 to 4 hours. The venous pressure reaches its greatest height in about 15 minutes. Similar results were obtained in inflammation produced by exposure to temperatures of 50° to 60° C. over longer periods of time. A rise in protein content of lymph was noted. According to the authors, lymph pressure cannot be measured in a normal leg.

Studies on Gonococcus.—The failure to obtain growth on plain agar is commonly used as a criterion of the Gonococcus. SEGAWA (*Centralbl. f. Bakt.*, 1932, **124**, 261), however, has shown that Gonococcus adapts itself and grows readily and in series on this simple medium when it has been transferred at least ten times on blood agar after isolation. He further found that this organism lived very much longer on plain agar either in a moist chamber or in the ordinary incubator than on blood agar. He emphasized the advantage of using such cultures for immunizing rabbits and in preparing vaccines because of the absence of the blood proteins and, using suspensions from agar cultures, he was unable to detect any varieties among thirty-five strains of gonococci which he studied by agglutination methods (p. 266) nor could he find any relationship between gonococci and any of ten differentiated meningococcus strains (p. 268). There is the possibility in the Reviewer's opinion that gonococci so adapted to grow on such an unnatural medium as plain agar may have lost in type specificity even if types of gonococci do exist which is at present unsettled.

Experimentally Induced Varieties of Pneumococci.—In the present-day state of confusion regarding the limitations in the transformation of bacterial types and of readiness to accept hypotheses based on the results obtained by experimental methods *in vitro* and in animals and applying these directly to epidemiologic and pathogenic studies in man, it is well to realize the difficulties in obtaining reliable facts. KLUMPEN (*Centralbl. f. Bakt.*, 1932, **124**, 241) has systematically studied the pneumococci and the methods used for inducing variations. The addition of antiserum or small pieces of the organs of animals heated to 56° C. for 1 hour to broth cultures were the two procedures which gave uniform results. The use of optochin, yeast and optochin, bile, the picking of daughter colonies or other methods were not regular nor reliable. He improved the antiserum technique by making 4- to 6-day instead of daily transfers. Mere colony appearances of which he described a number of forms were not found to be reliable. The changes he observed never went beyond the R (rough) form, were induced by measurable injury, and consisted in loss of type specific characters, virulence and

the facility to produce capsules, but the characteristics of true pneumococci such as morphology, bile sensitivity, behavior in litmus milk, etc., were retained so that they could not be confused with such organisms as the mouth streptococci. He could not support the view that pneumococci change during convalescence from pneumococcal infections into the R form in that he was unable to demonstrate in material from healthy, sick and convalescent persons any organisms which behaved biologically like the experimentally induced R forms of true pneumococci. The virulence he believed was probably of more importance in human epidemiology and pathogenicity than the type of pneumococcus, although Types I, II and III are generally of higher virulence than the group X organisms.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Comparison of Trachoma Virulence in Different Sections of the United States.—RICE, SMITH and SORY (*Pub. Health Rep.*, 1932, **47**, 1149) note that the virulence of trachoma never has received the attention it deserves, usually the percentage of the infected in a population being stated without reference to damage done. Severity is not to be measured by deaths but by the amount of blindness and number of entropions. On this basis the disease was found to be as follows:

	No. of cases.	No. of entropions to each 100 cases of trachoma.	No. of blind eyes to each 100 cases of trachoma.
Missouri	1609	43.4	8.2
Arkansas	1037	29.7	7.4
Kentucky	5846	10.8	5.8
Tennessee	1825	6.1	1.2
South Georgia	708	1.1	0.28

Hardening Procedures and Upper Respiratory Disease (Common Cold).—GAFAFER (*Am. J. Hyg.*, 1932, **16**, 233) observed over 300 adults for 35 weeks from September 29, 1929, to May 31, 1930, when every effort was made to secure reports of all attacks of upper respiratory disease (common cold). The group that during the winter slept with windows partially open, and the group that slept with windows wide open showed no significant difference in respect of (*a*) frequency and (*b*) severity of attack of upper respiratory disease (common cold). In respect of type of attack it was found that of the two groups the second (wide open windows) suffered relatively (*a*) fewer attacks with coryza and sore throat, and no cough; (*b*) more attacks with coryza, cough

and sore throat, and (*c*) more attacks with cough. The group that exercised outdoors less than 8 hours per week in the summer, and the group that exercised 8 or more hours per week, showed no significant difference in respect of (*a*) frequency, (*b*) severity, and (*c*) type of attack of upper respiratory disease (common cold). The group that exercised outdoors less than 4 hours per week in the winter, and the group that exercised 4 or more hours per week, showed no significant difference in respect of (*a*) frequency, (*b*) severity, and (*c*) type of attack of upper respiratory disease (common cold).

Relation Between Size of Frontal Nasal Sinuses and (1) Attacks of Upper Respiratory Disease (Common Cold) and (2) Certain Nose and Throat Conditions.—PALMER (*Am. J. Hyg.*, 1932, **16**, 224) found no evidence of association between size of frontal sinus and (*a*) number of attacks of upper respiratory disease (common cold), (*b*) duration of upper respiratory attacks (common cold), and (*c*) the presence or absence of any one of twelve recorded conditions of the upper respiratory passages.

Endemic Typhus Fever of the United States.—DYER *et al.* (*J. Infect. Dis.*, 1932, **51**, 137) state that the rat flea (Xenopsylla cheopis) as a vector of endemic typhus meets the requirements of the epidemiologic evidence. The virus of endemic typhus has been recovered repeatedly from rat fleas taken at typhus foci, and finally experimental transmission of the virus from rat to rat by means of rat fleas has been carried out in the laboratory. The foregoing evidence points to the rat flea (Xenopsylla cheopis) as a common vector of endemic typhus from rat to rat and from rat to man. The possibility must be borne in mind that rodents may be an important reservoir of typhus in parts of the world where epidemics of typhus occur, and it seems a reasonable hypothesis that epidemics of louse-borne typhus may have their origin from typhus transmitted from rat to man by rat fleas.

Is the "Appalling Increase" in Heart Disease Real?—BOLDUAN and BOLDUAN (*J. Prev. Med.*, 1932, **6**, 321) made a study of New York City's mortality statistics to determine the truth of the statements that there has been an "appalling increase in the death rate of heart disease." The character of the basic data (death certificates) is analyzed and sources of errors to be guarded against are pointed out. The difficulty of classifying deaths in which there is more than one cause of death is discussed, and the practice of statistical offices is described. The pathologic changes and the etiologic factors in heart disease are shown not to be limited to the heart, but to include also the arteries and kidneys. The *registered* increase in heart disease is admitted and shown to be accompanied in New York City by a registered decrease in apoplexy, Bright's disease and deaths charged to senility. Statistics are presented which show that in New York City, for the population as a whole, the death rate from cardio-arterio-renal disease is no higher now than it was 30 years ago. Similar statistics are presented for the four important age groups, and only in the group aged 65 years and over do these show any increase in the death rate from cardio-arterio-renal disease.

Typhus Fever. The Multiplication of the Virus of Endemic Typhus in the Rat Flea Xenopsylla Cheopis.—DYER and his associates (*Pub. Health Rep.*, 1932, **47**, 987) show by inoculation tests on guinea pigs that the virus of typhus multiplies enormously in fleas. While the whole of a recently infected flea might contain enough virus to infect a guinea pig one day after the flea had taken an infective feeding, after an interval of 40 days 1/128000 part of a flea was sufficient, showing enormous multiplication of the virus.

The Experimental Transmission of Endemic Typhus Fever of the United States by the Rat Flea Ceratophyllus Fasciatus.—DYER and his associates (*Pub. Health Rep.*, 1932, **47**, 931) had previously shown that two species of rat fleas, Xenopsylla cheopis and Ceratophyllus fasciatus, were incriminated in the transmission of typhus from rat to rat and from rat to man. In the present report this latter named flea, C. fasciatus, is definitely proven to have carried the infection. The evidence is fortified by clinical, cultural, microscopic, serologic, pathologic, and cross immunity tests.

The Standardization of Scarlet Fever Streptococcus Antitoxin. A Method Employing the Ear of the White Rabbit.—VELDEE (*Pub. Health Rep.*, 1932, **47**, 1043) undertook a study to determine the feasibility of using a laboratory animal in place of human subjects for the titration of scarlet fever antitoxin. The test worked out is performed in white rabbits, the inner side of the ear being utilized. An especially prepared and purified toxin of the scarlet fever streptococcus is used. Antitoxin prepared by using different antigens gave rather varying results in the tests, as is also the case when human test subjects are used.

Flocculating Tests for the Differential Diagnosis of Smallpox and Chickenpox.—HAVENS and MAYFIELD (*J. Infec. Dis.*, 1932, **50**, 242) found flocculation tests with 38 serums in 35 cases of smallpox to give positive results with all but 5. Four of these negative specimens were taken during the first week of the disease. Two cases in which successive specimens were obtained showed an increase in titer during the course of the disease. Eight serums in 7 cases of chickenpox gave negative results. Flocculation tests with smallpox scabs and immune rabbit serum gave definitely positive results with dilutions of the antigens as high as 1 to 2000. Chickenpox scabs invariably failed to flocculate in dilutions higher than 1 to 500. The flocculation obtained with lower dilutions of the chickenpox antigens occurred also with normal rabbit serum, and its nonspecific character was further demonstrated by absorption of the serum with staphylococci present in the scabs.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 16, 1933.

Some Studies on Peptone.—CARL J. BUCHER (Laboratory of Bacteriology, Jefferson Medical College). 1. A chemical analysis was made

of five brands of commercial peptone, designated B, W, P, F, and C., to determine the total nitrogen, nonprotein nitrogen, protein nitrogen, polypeptid nitrogen, amino-acid nitrogen and ammonia, the chlorid content and reducing substances (sugar). Peptone B contained the largest amount of total nitrogen, polypeptid nitrogen, nonprotein nitrogen, and the least amount of protein nitrogen. Peptone W contained the least amounts of total nitrogen, nonprotein nitrogen and polypeptid nitrogen, but the largest amount of protein nitrogen. The other three gave values between the two in the following order: C, F, and P. All contained chlorid. C and P peptones contained large amounts. B, C, and F contained reducing substances (sugar?).

2. Five media were made, each containing 20 gm. of one of the peptones, and enough of dibasic sodium phosphate, monobasic potassium sulphate to the liter, to give a pH value of 7.2 to 7.4. One cubic centimeter of a dilution of Bacillus coli containing equal numbers of organisms was seeded in each of 50 cc. portions of the five media. By dilution and plating, the growth curves for 24 hours on the five samples were made. The results were that in the W medium growth was slower but more abundant than in the others. The peak was reached about the 15th hour. In the F peptone medium there was a marked decrease in the number of the organisms in the 1st hour. The maximum growth was reached about the 11th hour in the B, P, F, and C media. The numbers of bacteria in the other four media at the maximum period of growth were between $10^{10.5}$ and 10^{11}.

3. Indol production on four strains of Bacillus coli was studied in samples of the peptone media after a 48-hour growth period. The F peptone medium gives the best positive test with vanillin and hydrochloric acid. B and P give results inferior to F, but superior to W. With non-indol-formers P and B give strongly positive tryptophane reactions.

4. Gas production on the several media was tested with one strain of Bacillus aërogenes and four strains of Bacillus coli. Gas was produced in small amounts in the Bacillus aërogenes culture and with three strains of Bacillus coli at the end of 48 hours.

5. Variations in the production of pigment by a number of chromogenes in the several media, in a 72-hour period, was not significant.

Changes in Blood Concentration Incident to Shock.—V. H. Moon and Patrick J. Kennedy (Laboratory of Pathology, Jefferson Medical College). Monographs on clinical pathology and microscopy contain no references to blood changes in traumatic shock or circulatory failure of similar character. Occasional references to such changes are found in clinical reports, but their significance and diagnostic importance have not been emphasized.

Observations by Cannon, Fraser, Hooper, Keith and others on wounded soldiers showed an increase in red cell count and hemoglobin and a decreased total blood volume due to loss of plasma, accompanying the development of shock. We verified this observation in experiments on dogs. Increased concentration of blood was found so regularly that it was employed as a criterion for shock in experiments already published.

Krogh, Lewis and others have shown that many types of capillary injury result in loss of tonus and increased permeability. Agents

such as light, heat, many organic and inorganic chemicals, bacterial products and products of cellular injury similar to histamin, will produce such capillary damage. Any of these appropriately applied will produce the shock syndrome. There is low temperature and blood pressure, rapid weak heart action, rapid respirations and death by circulatory failure. At postmortem there is marked capillary congestion of the viscera, especially in the pulmonary and gastrointestinal tracts, edema and petechial hemorrhages. Shock is due essentially to loss of capillary tonus.

We have observed the physiologic disturbances and postmortem changes characteristic of shock, in poisoning with barbital and other drugs, in mesenteric thrombosis, in influenza and other severe infections, in acute hemorrhagic pancreatitis, following burns and other severe intoxications. We have produced shock in dogs by various methods. In all instances there is a marked increase in the concentration of the blood as shown by specific gravity, red cell count and hemoglobin content.

Underhill emphasized increased concentration of blood as a feature of severe influenza, war-gas poisoning and of severe burns. De Takats and Mackenzie found it in 9 cases of acute hemorrhagic pancreatitis and proposed it as a test indicating the presence and the degree of shock.

Our observations indicate that circulatory failure resembling shock may develop in a wide variety of clinical conditions. An increased concentration of the blood, as shown by cell count, hemoglobin percentage and specific gravity, suggests that it is due to the same mechanism as traumatic shock. These observations may be helpful in clinical studies.

The Susceptibility of the Omentum of the Rabbit to a Single Exposure to Roentgen Rays (400 R).—Nicholas A. Michels (Daniel Baugh Institute of Anatomy, Jefferson Medical College). The animals were sacrificed at intervals from 5 to 96 hours after external exposure over the omental area. Factors: 200 K.V. 30 ma., 7½ min. S.T. 50 cm., field 6 by 8, filter 0.05 cu., 1 mm. al. The induced histologic changes were studied in whole-mount preparations of the omentum.

As a rule there occurred initial destruction of lymphoid cells, the duration of the degenerative phase varying from 5 to 45 hours after irradiation. Disintegration of lymphocytes and histiocytes occurred primarily in sites of their genesis, *viz.*, in milk spots, the process being accomplished by fragmentation of cytoplasm, dechromatization, fragmentation and dissolution of chromatin. The cellular débris was disposed by macrophages, many of which were of local origin, including mesothelium.

In early stages after irradiation (5 to 18 hours), omental capillaries were engorged with polymorphonuclear cells, a vast number of which migrated into the tissues where they disintegrated, presumably liberating a defense substance. Comparable extensive leukocytic infiltrations occurred in the lymph nodes and spleen.

Hemorrhages in omental capillaries occurred both in early (18 hours) and in late stages after irradiation (65 hours). Massive or diffuse in character, they were always accompanied by extensive blood stasis, agglutination of red cells, tortuosity, occlusion and degeneration of

capillaries. At times the capillary tortuosity was so pronounced that it led to the formation of broad blunt capillary stubs, which after being severed from the capillary bed constituted solid round capillary knots, the constituent cells of which degenerated.

Many instances of impairment and complete abolition of function in entire capillary tuft formations occurred 18 hours after irradiation, the endothelial cells of the peripheral capillaries dedifferentiating in mesenchyme.

The stimulating effect of a single small dose of Roentgen rays on lymphoid tissue manifested itself as early as 1 day after exposure and after 3 days reached such magnitude as to convert the omentum into a highly organized lymphoid organ in which the capillary vascularization was likewise enormously increased. By mitotic and amitotic proliferation the local mesothelium gave rise to 4 types of lymphoid follicles, *viz.*, solitary follicular, adventitial and mixed forms, many of which measured from 1 to 3 mm. in diameter.

A constant effect was the production of fibrosed areas in the omentum. Minimal after 5 hours, the process of fibrosis assumed larger proportions after 25 hours, was very pronounced and extensive after 65 to 77 hours and attained maximal density from 91 to 96 hours after exposure. Cell factors responsible for the fibrosis were primarily fibroblasts and mesothelium, secondarily endothelium and free lymphoid cells, including lymphocytes. Wide extension of a close-meshed capillary network was often the forestage of fibrosis in the sense that after cessation of the circulation the constituent endothelial cells became fibrilogenetic. These experiments provide confirmative evidence of the generally accepted biologic law that each variety of cell has a specific and selective sensitiveness to irradiation. The order of radiosensitiveness displayed by the omental connective tissue cells was as follows: lymphocytes, pseudoeosinophils, eosinophils, plasma cells, monocytes, endothelium, pericytes, fat cells, polyblasts or histiocytes, fibrocytes, mesothelium, mast cells, the latter being the most radioresistant, as their morphology was unaltered 91 hours after irradiation.

Opposed to Desjardin's recent contention that all stimulative changes induced by irradiation are essentially defense reactions or compensatory in character, this study shows that a single small dose of Roentgen rays causes a primary and direct acceleration of cellular metabolism on the omental cells.

Arterial and Venous Blood Sugar Response to Epinephrin in Normal Individuals and in Biliary Tract Disease.—A. CANTAROW (Laboratory of Biochemistry, Jefferson Hospital). This report consists of a study of the relationship between the concentration of glucose in capillary and venous blood before, and $\frac{1}{2}$, 1, $1\frac{1}{2}$ and $2\frac{1}{2}$ hours after the intramuscular administration of 15 minims of epinephrin to 33 individuals with and without disease of the liver and biliary passages. In each instance the fasting cutaneous and venous blood sugar concentrations were practically identical and were well within normal limits. The following changes occurred following the administration of epinephrin:

1. *Normal, 16 Cases* (no evidence of organic disease). Average maximum rise above resting level: (1) Capillary blood, 62 mg. per 100 cc.; (2) venous blood, 44 mg.; (3) arterial-venous difference, 31 mg.

2. *Catarrhal Jaundice, 4 Cases.* Average maximum rise above resting level: (1) Capillary blood, 29 mg. per 100 cc.; (2) venous blood, 24 mg.; (3) arterial-venous difference, 9 mg.

3. *Catarrhal Jaundice, Recovered, 3 Cases.* Average maximum rise above resting level: (1) Capillary blood, 61 mg. per 100 cc.; (2) venous blood, 38 mg.; (3) arterial-venous difference, 23 mg.

4. *Carcinoma of Liver, 4 Cases.* Average maximum rise above resting level: (1) Capillary blood, 14 mg. per 100 cc.; (2) venous blood, 11 mg.; (3) arterial-venous difference, 3 mg.

5. *Hepatitis, 2 Cases.* Average maximum rise above resting level: (1) Capillary blood, 16 mg. per 100 cc.; (2) venous blood, 11 mg.; (3) arterial-venous difference, 5 mg.

6. *Portal Cirrhosis, 3 Cases.* Average maximum rise above resting level: (1) Capillary blood, 22 mg. per 100 cc.; (2) venous blood, 18 mg.; (3) arterial-venous difference, 8 mg.

7. *Cholecystitis, 1 Case* (no jaundice). Average maximum rise above resting level: (1) Capillary blood, 17 mg. per 100 cc.; (2) venous blood, 12 mg.; (3) arterial-venous difference, 8 mg.

In the normal individuals and in those with catarrhal jaundice the maximum capillary and venous blood sugar levels were reached within 60 minutes while in those with hepatic carcinoma and hepatitis they were not reached until 90 minutes following the injection of epinephrin.

The interpretation of these data is difficult. It appears to be rather definitely established that epinephrin increases the mobilization of hepatic glycogen and decreases glucose utilization in the muscles and that normal epinephrin hyperglycemia results from the initial, transient hepatic glycogenolysis and is maintained by the decreased glucose utilization in the muscles. The subnormal blood sugar rise in hepatic disease may be due to either an insufficient quantity of glycogen in the liver or an increased tolerance to epinephrin. The subnormal arterial-venous difference may be due either to decreased glucose utilization in the muscles or to the relatively slight increase in the arterial blood sugar concentration, possibly below that required for the stimulation of active glucose utilization in the tissues.

Introduction to the Study of Purpura.—*A. Experimental Production of the Reactive Stage.* HAROLD W. JONES and LEANDRO M. TOCANTINS (Department of Medicine, Jefferson Medical College). From our studies of a large group of patients with purpura, we believe that all types are fundamentally similar, varying in degree of symptomatic expression only. Easy bruising, plus epistaxis, plus petechia, plus menorrhagia in normals may be related to acute purpura.

The fundamental pathologic factors in purpura are:

1. Mucous membrane disease.
2. Altered capillary hyperpermeability or fragility.
3. Platelet deficiency.

The contributing factors are:

1. Infection (tuberculosis and tonsillitis).
2. Glandular dysfunction (ovary and pituitary).
3. Toxic effects (heavy metals—disease as chronic nephritis, etc.).
4. Vitamin deficiency.
5. Allergy.
6. Heredity.

Platelet number, bleeding time length and development of hemorrhagic phenomena are variables which require experimental explanation. Clinical spontaneous cure is frequently seen. A great number of substances, such as iron, distilled water, etc., and methods such as purging, laying on of hands, anointing with holy water and hexing have produced such a cure.

Experimentally we were able for the first time to produce active purpura in dogs with as little as 1 cc. of antiplatelet serum injected either subcutaneously or intraperitoneally. All hemorrhagic features seen clinically have been observed in our animals with the exception of epistaxis. Skin petechia, ecchymosis, hemorrhage from the bowel, hematuria, hemorrhage into the peritoneum, iris, into the mucous membrane of the mouth, and conjunctival hemorrhage have been seen. Capillary resistance test and flicking test are positive. Bleeding time is greatly lengthened and the platelets are reduced.

Reactive Stage. Thirteen cubic centimeters of antiplatelet serum are injected either subcutaneously or intraperitoneally over a period of 13 days. Purpuric phenomena are present continually. Twenty-four to 48 hours after the last injection the hemorrhagic phenomena disappear. Following this there is a gradual platelet increase until the normal number is doubled, usually well over a million. At the height of the reactive stage, which varies in different dogs, and which may come at any time from 3 to 7 days after the last injection of antiplatelet serum, these phenomena are observed:

1. Inability to get blood for bleeding time by usual method.
2. Six to eight punctures must be made in order to obtain sufficient blood for red cell count.
3. There is hypercoagulability of the blood.
4. Rapid agglutination of platelets.
5. Tonicity of the skin is greatly increased.
6. Marked paling of mucous membranes of mouth and conjunctiva, probably due to capillary contraction.

The intensity of these phenomena gradually disappears over a period of 4 to 5 weeks. It is impossible during this reactive stage to produce purpura by the usual injections of antiplatelet serum.

We feel that the phenomena observed in this stage probably explain the development of the clinical spontaneous cure. An understanding of the mechanism of the production of the reactive stage will go far towards solving the problems surrounding the etiology and treatment of purpura.

Variations in Platelet Behavior After Intravenous Injection of Antiplatelet Serum in Dogs.—L. M. Tocantins and H. W. Jones (Department of Medicine, Jefferson Medical College). An antiplatelet serum was prepared by a series of injections of emulsions of dog's platelets into a rabbit. One cubic centimeter of this serum was injected intravenously into dogs weighing between 6.6 and 8.6 kilos, between 6 and 11 months of age. The platelets dropped below 50,000 within a few minutes and remained low for 48 hours. The animals developed purpura. The platelets began rising by the end of the second day and were back to normal 5 days after the injection. The curve of regenera-

tion of platelets after their destruction by antiplatelet serum follows very closely the curve found by Duke (1911) after almost complete defibrination of the blood of young dogs.

When the same dose of the serum was given to dogs that had received previous injections of the serum and had had purpura, no purpura was developed and the platelets rose from 68,000 to 500,000 2 hours after the injection and continued to rise. They reached their previous level of 950,000 in 3 days and climbed up to 1,170,000 9 days after the injection, then returning to normal.

The same dose of the serum was given to a dog with the spleen exteriorized. During the period when the platelets in the blood from the ear vein were at their lowest, the spleen showed strong contractions and was reduced to approximately two-thirds of its previous size. The platelet counts obtained by splenic punctures were higher by 100 to 200,000 during the strongest contractions. When the spleen enlarged again, the reverse took place. No purpura developed.

Conclusion. In dogs that have been prepared by previous injections of antiplatelet serum, the lowering of the platelet level by injection of 1 cc. of this serum intravenously is followed by a rapid regeneration of the platelets and reëstablishment of a normal level in a few hours. This response may be partly due to splenic action, but is probably dependent more on an increased ability of the previously injected animals to recuperate from destruction of their blood platelets. The animals that so behave are in the reactive stage and do not show purpura after doses of the serum, enough to produce purpura in similar animals not in that stage.

The intravenous injection of 1 cc. of antiplatelet serum, in not previously injected animals, constitutes a good method for the estimation of the value of therapeutic measures intended to influence the course of purpura, since all such animals behave alike after the injection insofar as the blood platelets, capillary resistance and bleeding time are concerned.

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